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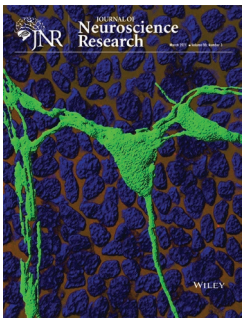
REVIEW



Severe acute respiratory syndrome coronavirus 2 infection reaches the human nervous system: How?

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Abstract

Without protective and/or therapeutic agents the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection known as coronavirus disease 2019 is quickly spreading worldwide. It has surprising transmissibility potential, since it could infect all ages, gender, and human sectors. It attacks respiratory, gastrointestinal, urinary, hepatic, and endovascular systems and can reach the peripheral nervous system (PNS) and central nervous system (CNS) through known and unknown mechanisms. The reports on the neurological manifestations and complications of the SARS-CoV-2 infection are increasing exponentially. Herein, we enumerate seven candidate routes, which the mature or immature SARS-CoV-2 components could use to reach the CNS and PNS, utilizing the within-body cross talk between organs. The majority of SARS-CoV-2–infected patients suffer from some neurological manifestations (e.g., confusion, anosmia, and ageusia). It seems that although the mature virus did not reach the CNS or PNS of the majority of patients, its unassembled components and/or the accompanying immune-mediated responses may be responsible for the observed neurological symptoms. The viral particles and/or its components have been specifically documented in endothelial cells of lung, kidney, skin, and CNS. This means that the blood–endothelial barrier may be considered as the main route for SARS-CoV-2 entry into the nervous system, with the barrier disruption being more logical than barrier permeability, as evidenced by postmortem analyses.

KEYWORDS

blood–brain barrier, bloodcerebrospinal-fluid-barrier, blood–nerve barrier, blood–nervous system barrier, COVID-19, double membrane vesicles cargo route, lymphatic brain drainage route, macrophage/monocytes cargo route, neurotropic virus, nicotinic acetylcholine receptor, olfactory route, peripheral nerve or neuronal retrograde route, SARS-CoV-2

1 | INTRODUCTION

A new, highly virulent coronavirus (CoV) capable of infecting humans (HCoV) currently holds much of the world's population hostage. This virus, referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causing the coronavirus disease 2019 (COVID-19) disease in infected subjects, emerged at the end of 2019 in China and the moment is affecting the population in at least 214 countries and territories around the world. This is only the latest in a series of lethal HCoV-caused illnesses, following the emergence of SARS-CoV

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in 2002 and Middle East respiratory syndrome-coronavirus (MERS-CoV) in 2012. Within the worldwide storm caused by the COVID-19 outbreak, most patients infected with SARS-CoV-2 and diagnosed with COVID-19 have only mild symptoms or are entirely asymptomatic. Unfortunately, approximately 20% of infected individuals exhibit far more serious symptoms, with 15% being considered "severe" and requiring oxygen, and the remaining 5% being viewed as "critical" and relying on ventilators. Symptoms of these serious cases include signs similar to pneumonia, septic shock, respiratory failure, and even multi-organ failure. Thus far, an estimated 1%–2% of COVID-19 cases have proven to be fatal (Guan et al., 2020; Li, Guan, et al., 2020), though it must be noted that the majority of fatalities associated with the disease happened in individuals suffering from chronic afflictions, including various cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and other comorbidities (Wu & McGoogan, 2020).

Analyses of deceased SARS-CoV-2 patients have shown that the viral particles reach and are distributed in nervous system tissues (Table 1). This discovery begs several important questions: from where did SARS-CoV-2 come to the nervous system and how did it access the brain? What are the brain infection manifestations? Is viral infection persistent in the brain? Are COVID-19 deaths dependent or independent on brain infection? The goal of this work is to get some logical answers to some of these questions.

To this end, we conducted a comprehensive analysis of existing literature, using the following search strategy and selection criteria. References for this review were collected through searches of PubMed, SCOPUS, and Web of Science for articles published until 10 July 2020. The search terms used were "coronaviruses, SARS-CoV, SARS-CoV-2, 2019-nCov, MERS-CoV, 229E-CoV", and "COVID-19", combined with "nervous system", "neuroinvasion", "neurological manifestation", and "brain." *In vitro* studies on neurotropism potentials of CoV on neural or glial cell cultures were considered. *In vivo* model investigations were included for infection routes (intranasal and intraperitoneal) of neuroinvasion. Postmortem autopsies and biopsy analyses were considered. Furthermore, clinical findings were searched and included for neurological signs related to CoVs infections.

Although the 2002–2004 outbreak of the SARS-CoV, as well as the 2012–2020 outbreak of the MERS-CoV and current COVID-19 are the real newsmakers, it is recognized now that in addition to SARS-CoV, MERS-CoV, and SARS-CoV-2 (all are β-CoVs of the B and C lineage), there are four other CoVs capable of infecting humans (HCoVs), which circulate continuously in the human population. These are HCoV-OC43 (Bruckova et al., 1970; Zhu et al., 2018) and HCoV-HKU1 (Woo et al., 2005) (β-CoVs of the A lineage or β1CoVs), and HCoV-229E (Hierholzer, 1976; Kaye et al., 1972) and HCoV-NL63 (Fouchier et al., 2004; van der Hoek et al., 2004) (α-CoVs). Identified in the late 1960s (HCoV-229E and the HCoV-OC43) (Almeida & Tyrrell, 1967; Bradburne et al., 1967; Hamre & Procknow, 1966; Larson et al., 1980; McIntosh et al., 1967) and in 2004–2005 (HCoV-NL63 (Esper et al., 2005; Fouchier et al., 2004; van der Hoek et al., 2004) and HCoV-HKU1 (Woo et al., 2005)), these HCoVs are known to be responsible for 3%–10% cases of the common cold and short-term upper respiratory infections that occur mainly in winter, with a short incubation time (Gerna et al., 2006, 2007), with about 2% of the human population being healthy carriers of an HCoV (Geller et al., 2012; Zumla et al., 2016). Although these HCoV strains can also cause more serious diseases of the lower respiratory tract, such as bronchitis, bronchiolitis, and pneumonia, especially in newborns or infants, elderly people, and immunocompromised patients (Geller et al., 2012; Zumla et al., 2016), their phenotypes are generally mild, and as a result, these four HCoVs received relatively little attention. Consequently, there is abundant research into CoV that stems all the way back to the 1930s, which has resulted in a considerable knowledge base and various tools for further examining these pathogens in humans.

Data from the *in vitro* experiments on culturing SARS-CoV and SARS-CoV-2 on the cell lines derived from different human and animal organs clearly indicated that there are many similarities as well as differences between these two CoVs. One of the interesting points made in this study was that SARS-CoV-2 (but not SARS-CoV) was able to modestly replicate in the neuronal (U251) cells, which highlighted the potential of this virus to cause neurological manifestations (e.g., confusion, anosmia, and ageusia) in patients with COVID-19 (Chu et al., 2020). The same study also showed that the pluripotent stem cell (iPSC)-derived BrainSphere model can be infected with SARS-CoV-2 (SARS-CoV-2/Wuhan-1/2020), which exponentially replicated 10-fold there (Bullen et al., 2020). The virus particles were found in the neuronal cell body extending into apparent neurite structures. This neural cell model expressed angiotensin-converting enzyme-2 (ACE2, a SARS-CoV-2 receptor on the surface of the host cells interacting with the viral spike (S) protein) but not the transmembrane serine protease-2 (TMPRSS2, the catalytic enzyme responsible for the S protein priming required for the subsequent CoV cell entry), which suggests the presence of alternative proteolytic tools there (Bullen et al., 2020). This state-of-the-art 3D organotypic cell culture model was already successfully

Significance

There are neurological manifestations and complications of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, similar to other coronaviruses SARS-CoV-2 is a neurotropic virus. To answer the question on how SARS-CoV-2 infection can reach the human nervous system, we are discussing here seven candidate routes. Among these seven pathways, the blood–endothelial barrier is the main route for SARS-CoV-2 entry into the nervous system. An important other route is breaching of the BBB, permeability of which can be increased by the cytokine storm leading to neuroinflammation.

TABLE 1 Ultrastructure features of SARS-CoV-2 viral particles in human nervous tissues and endothelial system

Ref.	Sample type	Sample source	Viral particle size	Virus features
Paniz-Mondolfi et al. (2020)	Postmortem	Frontal lobe tissue	80–110 nm	Two morphologically distinct types of spike protein structures, typical of β-coronaviruses, viral particles in frontal lobe brain sections. Individual and in small vesicles of endothelial cells of a pleomorphic spherical viral-like particles were observed. Blebbing of viral-like particles coming in/out of the endothelial wall which pointing to presumed active pathogen entry-transit (transcellular penetration) across the brain microvascular endothelial cells into the neural niche was recorded. Neural cell bodies exhibited distended cytoplasmic vacuoles containing enveloped viral particle exhibiting electron dense centers with distinct stalk-like peplomeric projections
Bulfamante et al. (2020)	Autopsy within three hours postmortem	Human olfactory nerve, gyrus, and brainstem	98–160 nm	Spherical particle with crown-like shape and inner dense core and electron-dense periphery, double nuclear envelope, severe damage in the olfactory nerve, autophagy phenomena appeared in the cytoplasm
Xu et al. (2005)[a]	Postmortem autopsy	Autopsy brain tissue was cultured with Vero E6 for E.M.	~80–90 nm (for SARS-CoV-1)	Clear cytopathic effect, enveloped virus particles with morphology compatible with coronavirus., Extracellular particles were found clustering and adhering to the surface of the plasma membrane, the immunostaining demonstrated that monokine induced by interferon-γ (Mig) expressed in gliocytes with the infiltration of CD68+ monocytes/macrophages and CD3+ T lymphocytes in the brain mesenchyme
Varga et al. (2020b)	Postmortem autopsy	Human-transplanted kidney	150 nm	Viral inclusion bodies in peipenilubular space and viral particles in endothelial cells, aggregates of viral particles with dense circular surface and lucid center, capillaries containing viral particles
Colmenero et al. (2020)	Skin biopsies	Human chilblains	92.26 nm	Immunohistochemistry and transmission electron microscopy presented the viral particles within endothelial cells in lesion skin biopsies from patients presenting with chilblains. Ultrastructural examination revealed the presence of round membrane-bound structures within the cytoplasm of endothelial cells showing an electro-lucent center, and surrounded by tiny spikes, giving them a halo-like appearance. Their mean diameter was 92.26 nm (80.76–109.76 nm), and the mean thickness of the spikes was 13.18 nm (12.36–13.88 nm)
Ackermann et al. (2020)	Pulmonary autopsy	Human pulmonary	60–150 nm	SARS-CoV-2 particles within the destructed lung vascular endothelial cell, which expressed 8.3-fold more ACE2 than non-COVID-19 samples. A total of 79 inflammation-related genes were differentially regulated only in specimens from patients with COVID-19

[a]Although this study is related to SARS-CoV and not to SARS-CoV-2, it is counted in here, since this work includes an immunostaining analysis.

used in the infection studies with the Zika, Dengue, HIV, and John Cunningham (JV) viruses. The most interesting point of these studies was the fact that the functional blood–brain barrier (BBB) had lost its functionality when microglia (which was not derived from the neural precursor cells but from the mesoderm germ layer) invaded the developing brain from the blood, resulting in cytokine release and neuronal damage in models analyzing the infection with HIV and JC viruses (Bullen et al., 2020). Therefore, one of the reasons why some, but not all, of the patients showed neurological manifestations could be related to the fact that the BBB normally hinders virus entry, but is impaired in some by inflammatory conditions (Bullen et al., 2020).

2 | ARE HUMAN CORONAVIRUSES NEUROTROPIC?

Neurotropism of HCoVs represents an interesting problem. Data on the immune-mediated central nervous system (CNS) pathology associated with viral infection are traditionally derived from the analysis of mice infected with a member of the *Coronaviridae* family, Murine Hepatitis Virus (MHV) strains, which is a β-coronavirus genetically related to Human CoV-OC4347 (Lane & Hosking, 2010). Being a group II coronavirus, MHV represents a natural pathogen of mice that typically infects the liver, gastrointestinal (GI) tract, and CNS, and shows various disease manifestations ranging from gastroenteritis to hepatitis and acute and chronic encephalomyelitis (Bailey et al., 1949; Cheever et al. 1949; Holmes & Lai, 1996; McIntosh, 1996; Perlman et al., 1999). It is recognized that there are at least three major mechanisms of the formation of immune-mediated lesions in CNS. They include: (a) a systemic inflammatory response syndrome which occurs as a result of an excessive host response to the infection and leads to the dysfunction of various organs, including CNS, (b) a direct viral infection of CNS immune cells, such as astrocytes, microglia, and macrophages, leading to the local production of pro-inflammatory cytokines IL-6, TNF-α, IL-1β, and IL12, as well as some toxic agents or subsequent tissue damage via the recruitment and activation of other immune cells and induction of apoptosis (Li et al., 2004), and (c) generation of an autoimmune reaction by an adaptive immune response directed against host epitopes or proteins, which are either misrecognized by the pathogen-directed antibodies or expressed by damaged tissues (and previously unrecognized by the adaptive immune system) (Bergmann et al., 2006; Natoli et al., 2020; Perlman & Dandekar, 2005). There is also a possibility for the eventual demyelination caused by immune-mediated events, either through T cells or by means of other cytokine and chemokine pathways (Wu et al., 2000).

About 40% (167 out of 417) of COVID-19 patients are known to develop a spectrum of neurological symptoms, such as cerebrovascular diseases, hypoxic/ischemic encephalopathy, impaired consciousness, acute cerebrovascular disease, encephalopathy, acute hemorrhagic necrotizing, corticospinal tract signs, and prominent agitation and confusion (von Weyhern et al., 2020) (reviewed in (De Felice et al., 2020)). These manifestations prove the presence of a link between the SARS-CoV-2 infection and CNS pathologies and support neurotropism of this virus (Puelles et al., 2020; Solomon et al., 2020).

Although the CoVs are not primarily neurotropic viruses and the most published reports defined the respiratory epithelium as their primary target, there is increasing evidence that neurotropism is indeed a common feature of the viruses (Chen, Zhou, et al., 2020; Glass et al., 2004; Khan et al., 2020; Li et al., 2012; Wang, Hu, et al., 2020). In addition to the aforementioned MHV, many other members of the β-CoV family have been documented to show neurotropism. This necessitates gaining a clear understanding of whether SARS-CoV-2 can enter the CNS and cause neuronal injury that may result in acute respiratory distress (Li et al., 2020) and potentially some other neurological manifestations.

3 | SARS-CoV

Human tissue studies displayed an abundance of ACE2 receptors in the epithelia of the small intestine and lung. These receptors were also identified in vesicular systems, such as venous and arterial endothelial cells (ECs) and arterial smooth muscle cells in all organs studied, including the brain (Hamming et al., 2004). In agreement with these observations, ACE2 immunostaining was widely distributed throughout the brain in the transgenic mouse (K18-hACE2 model) expressing human ACE2 (Doobay et al., 2007). A close look at the antigen and viral kinetics of the SARS-CoV virus in transgenic mice revealed that the infection began in the respiratory epithelium, spread rapidly to the alveoli, entered the brain via the olfactory nerve, and progressively invaded cortical and subcortical regions (McCray et al., 2007; Netland et al., 2008). It was also shown that, eventually, the infection extended to several vital brainstem nuclei, such as the nucleus *tractus solitarii*, dorsal motor nucleus of the vagus, and area postrema. Since the dorsal vagal complex (DVC) is located in the medulla oblongata, the lowest region of the brainstem that controls several autonomic activities, including orchestration of the cardiorespiratory function (heart and breathing) and food intake, injuries of this specific region of the brainstem could be detrimental to the maintenance of homeostasis and explain the cardiorespiratory disorder. Although the animals intracranially inoculated with low-dose virus were characterized by a limited viral spreading, they rapidly succumbed to infection (Netland et al., 2008). In animal models, CoV infection was accompanied by a considerable infiltration of lymphocytes and macrophages in the lungs, resulting in a release of pro-inflammatory cytokines. This occurred in the brain as well as at the pulmonary level, and within 5 days the subject mice entered a lethargic-like state, which would suggest the involvement of the CNS (McCray et al., 2007; Natoli et al., 2020). These neuroanatomic seem to point to the idea that the infected organisms die as a result of dysfunction of the cardiorespiratory center in the brainstem (Li, Bai, et al., 2020). In the past, autopsy results of humans with SARS-CoV infections showed strong evidence

of the presence of SARS-CoV by immunohistochemistry, real-time reverse transcription PCR, and electron microscopy (Natoli et al., 2020). Furthermore, individuals with acute SARS-CoV also exhibited the presence of the virus in the cerebrospinal fluid (CSF, Netland et al., 2008).

4 | MERS-CoV

Very limited data are currently available on the neurological disorders and pathology in humans with the MERS-CoV infection. Although the majority of patients infected with MERS-CoV exhibit predominant pulmonary clinical involvement, there are some patients who exhibit neurologic manifestations, such as ataxia, coma, peripheral nerve symptoms, and focal motor deficits (Arabi et al., 2015; Kim et al., 2017; Natoli et al., 2020). *Ex vivo* analyses of the MERS-CoV infectivity in various human lung cell lines demonstrated that the virus could infect human neuronal lines (Chan et al., 2013). In the hDPP4 transgenic mice model, intranasal MERS-CoV inoculation resulted in infection of both lung and brain by the virus at 3- to 9-day and 7- to 9-day postinoculation, respectively, indicating different viral infection kinetics (Hao et al., 2019). This may indicate a hematogeneous infection route. The brain is (possibly) infected via the olfactory nerves, and thereafter infection is rapidly spread to some specific brain areas, including the thalamus and brainstem (Netland et al., 2008). Interestingly, the virus particles were detected only in the brain, but not in the lung, in mice infected with low inoculum doses of MERS-CoV, suggesting that the infection in the CNS played a greater role in the high mortality (Li et al., 2016). Similar to SARS-CoV, MERS-CoV is also known to replicate in human macrophages and dendritic cells, lending additional support to the hematogeneous hypothesis (Zhou et al., 2014). The infected model brain consequences included a mild perivascular cuffing (Agrawal et al., 2015), and congestion and dilatation of the cerebral vessels and areas of cellular necrosis in the thalamus, hippocampus, and cerebral cortex (Hao et al., 2019; Natoli et al., 2020).

5 | SARS-CoV-2 (COVID-19)

Although the SARS-CoV-2 is mainly a respiratory pathogen, it can also manifest neurologically, causing encephalitis and epileptic seizures, which makes CNS involvement likely. The reported neurological sequelae of SARS-CoV-2 further suggest that the neurological impact of the virus needs to be examined. In fact, although the ongoing COVID-19 pandemic is still relatively young, it has already given rise to many neurological and neuroradiological phenotypes, including ageusia, anosmia, Guillain-Barré syndrome, and even acute necrotizing hemorrhagic encephalopathy (Mao et al., 2020; Poyiadji et al., 2020; Solomon et al., 2020; Zhao et al., 2020).

Mao et al. recently reported that among the patients with a severe form of COVID-19, more than 88% (78/88) displayed some form of neurologic dysfunction, such as acute cerebrovascular diseases and impaired consciousness (Mao et al., 2020). Also, during the current SARS-CoV-2 outbreak, a COVID-19 patient was reported to have lost control over breathing (Li, Bai, et al., 2020). Since many COVID-19 patients suffer acute respiratory failure, clinicians and health-care professionals must separate them into cases that are either neurologically affected, or do not display any neurological deficits (Baig et al., 2020; Li, Bai, et al., 2020). It would therefore be beneficial to have a greater understanding of the possible neuroinvasion of the disease, as it can help in the treatment and prevention of respiratory failure related to SARS-CoV-2 (Li, Bai, et al., 2020).

In a recent report it was demonstrated that both human and mouse olfactory sensory neurons do not express the two key genes involved in SARS-CoV-2 entry, namely *TMPRSS243* and *ACE2* (Brann et al., 2020). However, the olfactory epithelial support cells and stem cells express both of these genes, similar to nasal respiratory epithelium cells (Brann et al., 2020). This suggests that the SARS-CoV-2 infection may possess mechanisms that lead to olfactory dysfunction, and also brings into question whether olfactory bulb can serve as an entry point for CoVs. (Brann et al., 2020; Natoli et al., 2020). Since the anosmia symptoms appeared in many SARS-CoV-2 infections, these important questions were raised (De Felice et al., 2020): Does anosmia represent an indication of a SARS-CoV-2 infection in the CNS, or it is a reflection of an impact on the peripheral nervous system (PNS)? Furthermore, can the olfactory or optic nerves act as conduits for SARS-CoV-2's entry into the CNS? These questions are also in line with the current lack of published data on human neuropathological manifestations of the SARS-CoV-2 infection.

6 | NEUROLOGICAL MANIFESTATIONS IN COVID-19 PATIENTS

It is accepted now that the SARS-CoV-2 can reach and be manifested in most human organs and tissues (Figure 1). Mao et al. (2020)

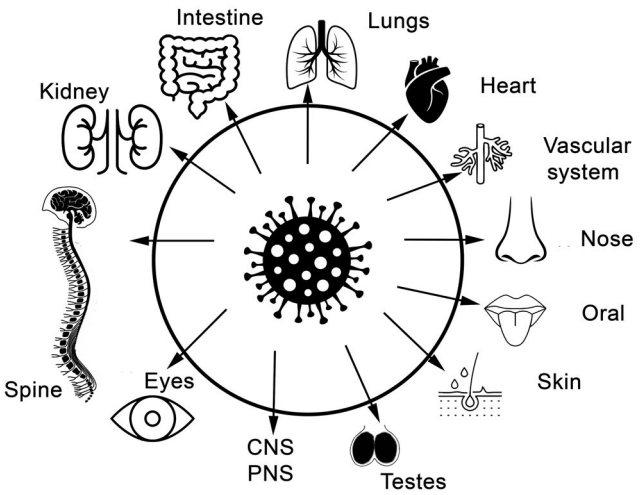

FIGURE 1 Respiratory and extra respiratory organ/system COVID-19 prevalence

and Solomon et al. (2020) investigated the penetration potential of the virus into the CNS in >220 patients (Mao et al., 2020; Solomon et al., 2020). Their results show that 36.4% of the patients had some neurologic abnormalities ranging from some nonspecific manifestations, such as headache, seizure, and dizziness to specific manifestations, such as stroke and loss of sense of taste (ageusia) and smell (anosmia) (Mao et al., 2020). In fact, gustatory and olfactory dysfunctions are both prevalent in patients with mild-to-moderate COVID-19, despite not having nasal symptoms, whereas some other neurological symptoms and manifestations can be seen in the more severe COVID-19 cases (Ahmad & Rathore, 2020; Asadi-Pooya & Simani, 2020; Conde Cardona et al., 2020; Lai et al., 2020; Vonck et al., 2020). It must be noted here that the more severe neurologic symptoms, such as decreased levels of consciousness, or development of seizures and stroke, were more common in patients in the late stages of the infection, and these symptoms were responsible for the heightened mortality rate in severely affected patients (Mao et al., 2020). Histopathological examination of the brain specimens obtained from 18 patients who died 0 to 32 days after the onset of the COVID-19 symptoms of COVID-19 showed only hypoxic changes and did not show encephalitis or other specific brain changes referable to the virus. There was no cytoplasmic viral staining in immunohistochemical analysis. The virus was detected at low levels in six brain sections obtained from five patients (Solomon et al., 2020).

One should keep in mind though that the diagnosis of coronavirus particles by electron microscopy is challenging due to the numerous similarly appearing normal cellular structures (e.g., clathrin-coated vesicles, which are normal cell organelles involved in intracellular transport or cross-sections of the rough endoplasmic reticulum), creating significant controversy (see e.g., (Miller & Brealey, 2020; Miller & Goldsmith, 2020; Su, Gao, et al., 2020; Su, Yang, et al., 2020) and (Goldsmith et al., 2020; Varga et al., 2020a, 2020b)). In fact, it was pointed out that "there are inherent difficulties in discrimination of cellular vesicles from viral particles solely by morphological evidence" (Su, Gao, et al., 2020). In other words, the electron microscopic evidence alone is not sufficient for unambiguous identification of virions, with many erroneously identified particles being found in incorrect cellular location, or lacking diagnostic features of coronavirus. We provided an in-depth discussion of this issue in our recent review (Elrashdy et al., 2020).

It was also hypothesized that CNS infection with involvement and dysfunction of the cardiorespiratory brainstem centers may contribute to the death of infected animals or patients (Li, Bai, et al., 2020; Xia & Lazartigues, 2008). hACE2 transgenic mice that inoculated intracranially or intranasally with virus particles commonly exhibited a disseminated infection of the DVC (area postrema, nucleus tractus solitarius, and dorsal motor nucleus of the vagus) (Netland et al., 2008). This complex contains efferent and afferent projections of the vagus nerve to the lungs and respiratory tracts, suggesting that the vagus nerve may also serve as a neuronal route for viral entry into the brain. This leads to the hypothesis that the dysfunction of the cardiorespiratory brainstem center may be at least partially responsible for the death of CoV-infected animals or patients (Li, Bai, et al., 2020; Xia & Lazartigues, 2008). A cytokine storm with excessive levels of pro-inflammatory cytokines (IL-6, GM-CSF, IL-2, interferon-γ, IL-7, inducible protein 10, TNF-α, macrophage inflammatory protein 1-α, monocyte chemoattractant protein 1, and monocyte chemoattractant protein 1) may also contribute to the lethality of the COVID-19 infection (Desforges et al., 2019; Mehta et al., 2020). This is illustrated by recent reports of a COVID-19 patient with an acute necrotizing encephalopathy, a rare complication observed in infections with viruses such as influenza, and related to a cytokine storm in the brain without direct viral invasion (Poyiadji et al., 2020; Vonck et al., 2020).

A postmortem histological analysis of the brain of a 71-year-old man who died from complications of COVID-19 revealed the presence of several types of pathological lesions, such as a widespread hemorrhagic and lesion of white matter with clusters of macrophages, necrotic blood vessels, and perivascular inflammation, acute axonal injury, demyelination, marked lesions of central axonal injury, associated extravasated blood, and surrounding myelin loss (Reichard et al., 2020). Despite all of these dramatic neurological manifestation in this patient, a routine histological examination of the olfactory bulb/nerve revealed only aging-related corpora amylacea (Reichard et al., 2020). More globally, the presence of brain tissue edema and partial neuronal degeneration were reported in autopsy reports of deceased COVID-19 patients (Xu, Shi, et al., 2020).

7 | SARS-CoV-2 CELLULAR ENTRY RECEPTORS

It appears that all the major requirements for efficient hijacking of the nervous cells/tissues by the SARS-CoV-2, which caused the COVID-19 outbreak, are in the place. This includes utilization of the ACE2 (which is present on the surfaces of the cells in a wide variety of human tissues, including the brain) as a cellular entry receptor and the presence of the spike glycoprotein possessing affinity for ACE2, which is ~10- to 20-fold higher than that of the SARS-CoV spike protein (Walls et al., 2020; Wrapp et al., 2020). All this indicates that SARS-CoV-2 may have higher neuroinvasive potential compared to previous HCoVs. It was also shown that the SARS-CoV-2 receptor ACE2 is expressed in ECs of cerebral capillaries, and within the brain parenchyma in both neurons and microglia (Yamagata et al., 2020). However, there is no complete expression profile of the catalytic enzymes that are required for CoV entry, such as transmembrane serine protease 2 (TMPRSS2) and Furin, on the surface of the nervous tissue cells, from where the COVID-19 can inter to the human nervous system.

Recent studies showed that a subset of COVID-19 patients exhibit altered olfactory function (Altin et al., 2020; Chung et al., 2020; Cooper et al., 2020). Single-cell and bulk RNA-Seq data sets from human nasal biopsy (Durante et al., 2020) were analyzed to identify the cell types in the human olfactory neuroepithelium (which is an extracranial site supplying input to the olfactory bulbs of the brain) and in the olfactory bulb that express cell entry molecules (ACE2

and TMPRSS2, as well as Furin) that mediate infection by SARS-CoV-2 (Brann et al., 2020). This was further complemented by the analysis of the single-cell RNA-Seq data from whole mouse olfactory bulb from juvenile mice (age postnatal day 26–29; Zeisel et al., 2018) as well as single-cell RNA-Seq data from the olfactory bulb from the adult male mice (8 to 12 weeks old) (Brann et al., 2020). These analyses revealed that two key genes involved in SARS-CoV-2 entry, namely ACE2 and TMPRSS2, were expressed in the samples from the whole olfactory mucosa in mouse and human in addition to the thiol proteases cathepsins Ctsb and Ctsl (Brann et al., 2020). However, neither olfactory sensory neurons nor olfactory bulb neurons expressed these genes (with the exception of cathepsins Ctsl), which instead were expressed in several stem, perivascular, and support cells (Brann et al., 2020). Such results suggest that anosmia and related disturbances in odor perception in COVID-19 patients could be associated with the SARS-CoV-2 infection of nonneuronal cell types (Brann et al., 2020).

Vavougios proposed that the furin-like cleavage site of the CoV spike protein could be an important determinant for the neurotropism of this virus (i.e., its ability to infect nerve tissue) (Vavougios, 2020a, 2020b). In fact, it was found that cleavage of the S-protein by furin or furin-like proteases is important for the invasion and virulence of SARS-CoV and MERS-CoV (Millet & Whittaker, 2015). Furthermore, the proteases determine the host tissue tropism and specificity of these CoVs (Millet & Whittaker, 2015), letting them infect the nervous system via membrane fusion. However, additional studies are necessary to determine if the furin-like cleavage site on the spike protein of SARS-CoV-2 plays a certain role in its invasion of the nervous system. Another important issue that also requires careful future analysis is the presence and sustainability of the nervous system damage after the cure of the COVID-19 infection. This became especially troublesome in light of the fact that the anosmia and ageusia, which are frequently observed among COVID-19 patients, also serve as characteristic and prodromal nonmotor manifestations of Parkinson's disease (Haehner et al., 2011; Oppo et al., 2020).

It is also possible that other SARS-CoV-2 receptors may exist, or another cellular entry mode is utilized by SARS-CoV-2 for hijacking the nervous cells/tissues. These possibilities were supported by Radzikowska et al. (2020), whose analysis suggested the presence of a different receptor repertoire potentially involved in the SARS-CoV-2 infection at the epithelial barriers and in the immune cells, such as the co-expression of ACE2, CD147 (BSG), and CD26 (DPP4). Changes in the expression of these receptors related to gender, age, smoking, and obesity, as well as to the status of the disease may further contribute to COVID-19 severity and morbidity patterns (Radzikowska et al., 2020). Using a combination of structural and molecular modeling approaches, Fantini et al. (2020) revealed that the sialic acids linked to host cell surface glycoproteins and ganglioside can also serve as an additional cellular entry route for SRSR-CoV-2 (Fantini et al., 2020), similar to influenza virus, SARS-CoV, and HCoV OC43 (Lu et al., 2008; Tortorici et al., 2019). A new type of ganglioside-binding domain (111–158) at the tip of the N-terminal domain of the SARS-CoV-2 S protein was identified, which is fully conserved among clinical isolates worldwide, and sialic acid and ganglioside bind chloroquine with high affinity (Fantini et al., 2020).

Although there is a 77% sequence identity between SARS-CoV and SARS-CoV-2, Hassanzadeh et al. (2020) discovered that the SARS-CoV-2 S protein has a slightly higher positive charge than SARS-CoV. This is because it has five less negatively charged residues and four more positively charged residues, which may be why the protein has a higher affinity for negatively charged regions of other molecules in both specific and nonspecific interactions (Hassanzadeh et al., 2020). Analysis of the peculiarities of the S protein binding to the host ACE2 receptor showed a 30% higher binding energy for SARS-CoV-2 than the SARS-CoV S protein (Hassanzadeh et al., 2020). Therefore, SARS-CoV-2 is expected to have higher efficiency than SARS-CoV in reaching the brain after entering through the cells (Hassanzadeh et al., 2020).

8 | CIGARETTE SMOKING, COVID-19 INFECTIVITY, AND NEUROTROPISM

Cigarette smoke has been shown to increase patient susceptibility to COVID-19, with smokers suffering from the disease being far more likely to develop critical illnesses (Guo, 2020; Patanavanich & Glantz, 2020; Zhao, Meng, et al., 2020). One study of 1,099 COVID-19 patients revealed that only 4.7% of nonsmokers required mechanical ventilation, were admitted to an intensive care unit, or died, compared to 12.3% of smokers (Guan et al., 2020). Although the exact mechanism for such an association is uncertain, one of the potential explanations can be found in the fact that cigarette smoke can increase the levels of ACE2 expression in the lungs of mammals (Smith & Sheltzer, 2020). In the case of SARS-CoV infection, ACE2 levels may influence the progression of the disease: within a group of mice engineered to express human ACE2, mice with the highest levels of ACE2 mRNA displaying the shortest survival time after being exposed to SARS-CoV (McCray et al., 2007).

In agreement with this model, analysis of the data sets of large, small, and bronchial airway epithelium of current and former smokers revealed a noticeable upregulation of pulmonary ACE2 gene expression in all data sets of smokers compared to nonsmokers, irrespective of tissue subset (Cai et al., 2020). Another study also showed that ACE2 expression in the lower airways is upregulated by active cigarette smoking and COPD, which might help explain the higher risk of serious COVID-19 in patients that smoke (Leung, Yang, et al., 2020). Interestingly, in this study, smoking status was significantly related to the levels of the ACE2 gene expression in the airways of these participants, where current smokers showed a significantly higher gene expression than never-smokers, whereas former smokers' levels were between current and never-smokers (Leung, Yang, et al., 2020). This ACE2 overexpression in human bronchial epithelial cells is mediated by nicotine exposure specifically through the α7 subtype of nicotine acetylcholine receptors (α7-nAChR) (Russo et al., 2020), which was significantly correlated with the expression of *CHRNA7* gene encoding the α7-nAChR. The

levels of the *CHRNA7* expression were also correlated with the body mass index, raising an intriguing scenario, where the nicotine receptor mediation of ACE2 may also be related to the high proportion of obese individuals among the COVID-19 cases (Leung et al., 2020). Further support is given by the fact that cigarette smoke might cause a dose-dependent upregulation of ACE2, in both rodent and human lungs (Smith et al., 2020).

There are also reports indicating that smoking may result in higher levels of androgen hormones like testosterone. The androgen receptor has been shown to increase the expression of TMPRSS2 (Qing et al., 2020), and sex steroid modulation of TMPRSS2 serves as a possible mechanism that may explain the differences in SARS-CoV-2 infection rates between females and males (Stopsack et al., 2020). In line with these observations, RNA-sequencing data analysis for lung and oral epithelial tissues of human COVID-19 patients clearly demonstrated that both TMPRSS2 and ACE2 were significantly upregulated among smokers versus nonsmokers (Chakladar et al., 2020). It was also found that there was a correlation between the smoking-mediated upregulation of the androgen pathway and the upregulation of ACE2/TMPRSS2 expression, and that the androgen receptor gene and ADAM17 (a key mediator of ACE2 activity) were upregulated in smokers (Chakladar et al., 2020). Furthermore, smoking was shown to induce furin upregulation, although to a lesser degree than ACE2 (Cai et al., 2020).

Taken together, these observations support the idea that epithelial cells may be more susceptible to the COVID-19 virus as a result of smoking (Chakladar et al., 2020). But what one can say about smoking and neurotropism of CoVs? ACE2 expression in human brain vessels was significantly elevated by cigarette smoke extract (CSE) treatment. Furthermore, it was found that ACE2 expression is increased in vessels exposed to diabetes or smoking and in ischemic brains, which leads to them being more susceptible to infection. Also, ACE2 expression was upregulated in primary cultured human blood vessels with diabetes when compared to healthy vessels (Choi et al., 2020). Therefore, the regulation of ACE2 expression by cigarette smoke in the brain likely has a significant effect on SARS-CoV-2 susceptibility, and might facilitate viral dissemination (Smith et al., 2020). The harmful effects of CSE on the BBB can upregulate several genes related to inflammation, such as *VCAM1* and *ICAM1*, which also have destructive effects on the BBB (Choi et al., 2020).

9 | NERVOUS SYSTEM ACCESS ROUTES OF HCOVS AND RELATED PATHOPHYSIOLOGY

CoVs are primarily not neurotropic viruses, and their primary target is the respiratory epithelium. However, although the ACE2, which serves as a major receptor for SARS-CoV and SARS-CoV-2, and which is an enzyme attached to the cell membranes of cells in the arteries, lungs, kidney, heart, and intestines, it can also be found in glial cells in spinal and brain neurons (Palasca et al., 2018). SARS-CoV and SARS-CoV-2 can therefore use these receptors to enter, attach, multiply, and damage the neuronal tissue. Studies on mice also show that SARS-CoV can enter the brain through the cribriform bone or through a retrograde transfer via the olfactory epithelium, and in 7 days can reach the brain. The virus can also enter the brain directly due to a disruption of the BBB during the viremia phase of the disease. The invasion of peripheral nerve terminals by CoV is another postulated mechanism, after which the virus enters the CNS through the synapse connected route. Given that SARS-CoV-2 is very similar to SARS-CoV, it is likely that it can invade the CNS using the same methods as SARS-CoV.

However, though the receptor's expression pattern can determine which cells can be infected, not all cells that express the receptor, or even cells with the highest receptor expression, are necessarily the primary targets of the viral attack. This can be exemplified by the mouse hepatitis virus (MHV) studies, where the MHVR receptor is highly expressed in the liver, but barely so in neurons. In contrast, the MHV strain JHM.SD, which is highly neurovirulent, is not able to replicate in the liver during viral infection, (Bender et al., 2010). Mapping the viral tropism *in vivo* and the virulence factors that contributed to pathogenesis required considerable time and energy. Surprisingly, it was revealed that tissue tropism was not solely impacted by the viral spike protein, but instead by other viral "background genes," such as replicase and nucleocapsid, in addition to different viral accessory genes, in which can also be used for the determination of tropism (reviewed in (Weiss & Leibowitz, 2011)). Pathogenesis can therefore not be directly inferred from the knowledge of the receptor and spike protein alone. Future studies on SARS-CoV-2 will define tissue tropism and whether it parallels SARS-CoV or not (Weiss, 2020).

Let us look more closely on the potential routes for SARS-CoV-2 entry into the CNS (see Figure 2). The observation of the presence of the viral-like particles in brain capillary endothelium and their active budding across the ECs strongly suggested that the hematogeneous route and the endothelial bed were the most likely pathway to the brain (Paniz-Mondolfi et al., 2020). Expression of the human receptor ACE2, which serves as a receptor and the binding target for the trimeric spike protein of SARS-CoV-2, by the vascular endothelium (Hamming et al., 2004) also supported this interpretation (Paniz-Mondolfi et al., 2020). However, other routes of the SARS-CoV-2 CNS entry, such as retrograde axonal transport from the olfactory bulb, cannot be ruled out. In line with this idea, there is experimental evidence showing the capability of neuroinvasion by HCoV-OC43 and SARS-CoV in mice infected intranasally with these viruses (Desforges et al., 2019). It was hypothesized that this could happen as a result of a disruption of the nasal epithelium and the resulting neuronal dissemination of the virus (Desforges et al., 2019). This idea would explain the onset of early signs of anosmia as a precursor to other neurological symptoms. Furthermore, based on the previously observed ability of other viruses such as SARS-CoV in the brainstem to induce the dysfunction of the cardiorespiratory center (Netland et al., 2008), it was hypothesized that the respiratory failure of COVID-19 patients may be governed by the neuroinvasive potential of SARS-CoV-2(Li, Bai, et al., 2020; Paniz-Mondolfi et al., 2020). Therefore,

COVID-19 might cause respiratory failure and death not through damage to the lungs, but by affecting the brain.

Baig et al. have suggested (Baig et al., 2020) that the SARS-CoV-2 may access the brain using the same "transcribrial route" defined for other pathogens that target the CNS (such as *Naegleria fowleri* causing meningoencephalitis) (Baig, 2016) and for the delivery of drugs and embryonic stem cells to brain (Baig, 2017). It is also likely that the SARS-CoV-2 dissemination across the cribriform plate of the ethmoid bone or in the systemic circulation may result in cerebral involvement, similar to what was reported in

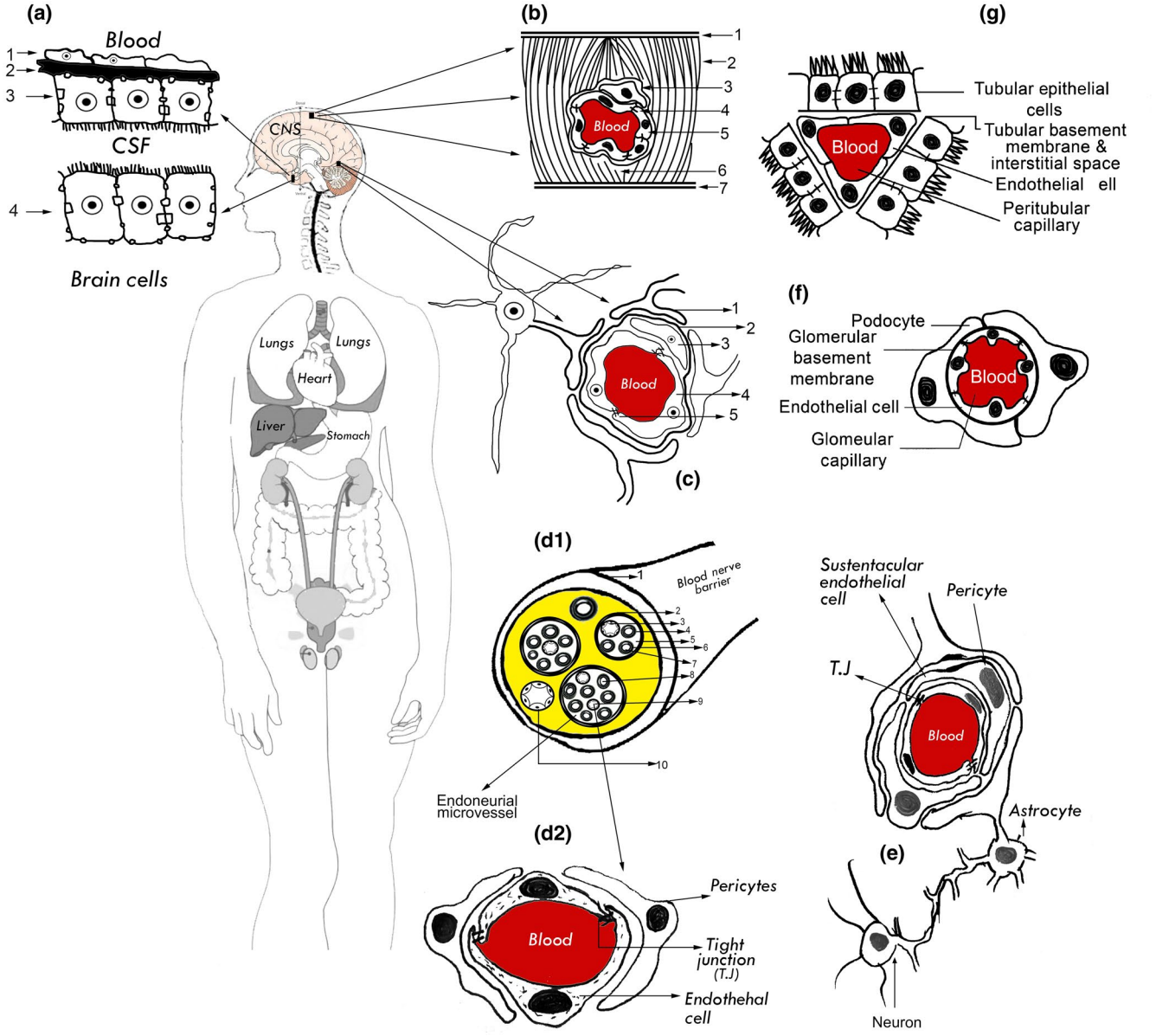

FIGURE 2 Diagram for human blood–nervous system barriers. (a) Blood–cerebrospinal fluid (BCSFB)/CP barrier (1. Fenestrated endothelium, 2. Interstitial matrix, 3 and 4. Choroid plexus epithelium, 5. Brain cells). (b) Blood–cerebrospinal fluid (BCSFB)/meningeal barrier (1. arachnoid, 2. Trabeculae cross-section, 3. Pericyte, 4. Epithelial cell tight junction, 5. Epithelial cell, 6. CSF, 7. Pia Mater). (c) Blood-brain barrier (1. Astrocyte, 2. Basement membrane, 3. Pericyte, 4. Endothelial cell [non-fenestrated], 5. Tight junction). (d1) Blood–nerve barrier BNB (cross section) (1. Epineurium, 2. Perineurium, 3. Endoneurial vessel, 4. Basal lamina. 5. Endoneurium, 6. Myelin, 7. Nucleus of Schwann cell, 8. Axon, 9. Endoneurial endothelial cells of microvessel, 10. Epineurium blood vessel). (d2) Blood–nerve barrier. (e) Blood olfactory nerve barrier. (f) Inside the glomeruli barriers both of glomerular endothelial and epithelial cells (known as podocytes) cross talk occurs, where they share the glomerular basement membrane. (g) inside the glomerular both of peritubular capillary endothelial and tubular epithelial cells cross talk also occurs through the barrier where they are separated by a tubular basement membrane and interstitial space. Both of kidney epithelial (podocytes and tubular) are breached with SARS-CoV-2 in COVID-19 patients (reviewed in (Elrashdy et al., 2020)). From her the viral and/or its components can spread from renal anastomosis into CNS via nerve supply. Although the cross talk between human organs in health and diseases is a very complicated processes go through huge number of mechanisms, but it well documented in a dramatically pattern (Armutcu, 2019; Lu et al., 2015) [Color figure can be viewed at wileyonlinelibrary.com]

patients affected by SARS-CoV (Netland et al., 2008). As per Baig et al., by virtue of its presence in general circulation, SARS-CoV-2 can be passed into cerebral circulation, where it will have a chance to interact with ACE2 expressed in the capillary endothelium, and thereby to infect cells there, causing damage to the endothelial lining and providing viral access to the brain (Baig et al., 2020). Importantly, SARS-CoV-2 interaction with the ACE2 receptors expressed in neurons can lead to virus entry and begin a cycle of viral budding and neuronal damage without substantial inflammation, as was reported previously in SARS-CoV cases (Netland et al., 2008). It should be noted that well before the anticipated neuronal damage occurs, the endothelial ruptures in cerebral capillaries, together with bleeding within the cerebral tissue, can be fatal in COVID-19 patients (Baig et al., 2020). SARS-CoV-2's movement to the brain via the cribriform plate located near the olfactory bulb can act as an additional path that would allow the virus to reach and affect the brain. All this clearly indicates that the observation of hyposmia or an altered sense of smell in an early and uncomplicated stage of a COVID-19 patient should be thoroughly investigated for CNS involvement (Baig et al., 2020).

10 | OLFACTORY ROUTE (OE)

There is a growing interest in the study of the OE. It is the most proximal axonal area of the human brain, with neurons that can be regenerated. Many studies show a strong link between olfactory deficiency (e.g., loss of smell) and neurodegenerative diseases such as (Alzheimer's and Parkinson's diseases, AD and PD, respectively). The main neurological manifestation of COVID-19 is the loss of taste or smell. Since most instances of smell loss occur without significant rhinorrhea or nasal congestion, the virus likely targets the chemical senses in ways that are different from those utilized by other common cold-causing agents or endemic coronaviruses (Cooper et al., 2020). Therefore, it seems that the olfactory route represents a logical pathway of SARS-CoV-2 entry into the CNS. In fact, analysis of SARS-CoV-2 prevalence in clinical specimens showed that the viral copy number found in nasal swabs is ~200-fold higher than those found in the bronchoalveolar lavage or pharyngeal swabs (Wang, Xu, et al., 2020; Zou et al., 2020). The utilization of the olfactory route is further supported by the fact that issues with smell have been reported internationally, reporting a prevalence as high as 85% in a large, multicenter European survey (Lechien et al., 2020). Furthermore, high-intensity ACE2 staining was detected in olfactory mucosal biopsies, with a 200- to 700-fold ACE2 enrichment in the olfactory neuroepithelium (sustentacular cells) relative to the nasal respiratory or tracheal epithelial cells (Chen, Shen, et al., 2020). This cellular tropism of SARS-CoV-2 may underlie its high transmissibility and association with dysfunction of olfactory neuroepithelium receptors in the nasal and oral mucosa, and also suggests the existence of a viral reservoir that may be a good candidate for intranasal therapy. In contrast, ACE2 was not found in immature and mature olfactory neurons (Chen, Shen, et al., 2020). Taken together, these observations of the enhanced expression of ACE2 localized to the olfactory neuroepithelium of the human airway suggests that COVID-19 infection and replication may take place in the apical layer of nasal and olfactory mucosa, resulting in olfactory loss and acting as a possible entry point of the virus into the CNS, causing neurological symptoms (Chen, Shen, et al., 2020; Mao et al., 2020). Furthermore, although the postmortem examination showed no inflammatory infiltrates or neuronal necrosis in the brains of the deceased COVID-19 patients analyzed histologically, and although the SARS-CoV-2 RNA copy numbers were predominantly low in the brain, the corresponding values detected in the olfactory bulb were higher than those in the brainstem, supporting the hypothesis of the viral entry into the brain via the lamina cribrosa (Menter et al., 2020). In light of the facts that the swabs from olfactory sustentacular cells bear ~200-fold SARS-CoV-2 RNA copy numbers compared to those found in the bronchoalveolar lavage, and that the olfactory sustentacular cells express 200- to 700-fold more ACE2 relative to the nasal respiratory or tracheal epithelial cells, a fundamental question arose: are there local structures responsible for the COVID-19-associated loss of smell and taste? This seems to be the case, since the microenvironment becomes favorable for the release and/or recruitment of inflammatory leukocytes and cytokines, and subsequently acute reversible or chronic impairment of these chemosensory functions (Cooper et al., 2020; Kirschenbaum et al., 2020; Schlosser et al., 2016; Torabi et al., 2020).

11 | BLOOD–NERVOUS SYSTEM BARRIERS (BNSBs)

Humans have evolved highly sophisticated barrier systems to prevent the entry of potentially harmful substances into the nervous system. The CNS contains four types of such barriers, which are the BBB, the choroid plexus (CP, which is a vascular tissue found in all cerebral ventricles that produces the CSF of the CNS) blood–cerebrospinal fluid barrier (BCSFB), the meningeal–brain barrier (which consists of the three membranes that envelop the brain and spinal cord, with the meninges in mammals being the dura mater, the arachnoid mater, and the pia mater), and the lymphatic vessel–brain barrier. In addition, there is one more barrier of the PNS, namely, the blood–nerve barrier (BNB). However, some viruses are able to directly manipulate the BBB or BCSFB to enter the CNS, whereas others hijack host immune cells or travel within peripheral nerves. The BNSB may represent the main route of the SARS-CoV-2 for breaching the nervous system (CNS and PNS).

The nervous system has barriers that isolate it from the bloodstream and help it achieve the complex microenvironment control necessary for complex neural signaling. Although all these main physiological nervous barriers differ in location, size, morphology, and function, their main structural units are the epithelial or ECs, which are known to express both ACE2 and TMPRSS2. The vascular

ECs constitute the interface between the interstitial fluid of the CNS tissue and the blood. The blood–cerebrospinal fluid barrier (BCSFB) comprises a single layer of endothelial/epithelial cells at the CP or meninges. It is a fluid–brain barrier consisting of two membranes that separate blood from CSF at the capillary level, and CSF from brain tissue. Epithelial cells separate the plexus or meningeal blood from the CSF. The BCSFB regulates most of the exchange of ions, water, and other substances that can be found between blood and CSF. A few localized brain regions, such as the pineal and the area postrema, are called circumventricular organs (CVOs) and lack the vascular BBB, but rather have a barrier of ependymal cells between the CSF and CVO tissue, and of tanycytes between adjacent brain tissue and the CVO. Therefore, the BCSFB represents a regulatory interface comprising a monolayer of cells that separates the blood from the fluids of the CNS (Abdul Razzak et al., 2019; Doran et al., 2013).

As most neurological disorders in COVID-19 patients are demonstrated in somewhat aged patients, the well-documented effects of age on the endothelial/epithelial barriers and specifically of the BNSB should be kept in mind. The exponential decline in integrity/permeability of these barriers is linked to age as reviewed in detail by Delaney and Cambell (2017). It is becoming increasingly evident that the pericytes are susceptible to age-dependent deterioration at the BBB. Breakdown of the paracellular pathway, pericyte loss, and transcellular permeability can exacerbate the events linked with age, and can lead to the extravasation of blood-borne material. The susceptibility of endothelium toward many intrinsic destructive agents is known to increase with aging (Delaney & Campbell, 2017). Again, these facts may provide some explanations of why the SARS-CoV-2 particles were detected in all postmortem nervous tissue biopsy examined (see Table 1).

11.1 | The blood-brain barrier route

The BBB, located in the brain microvessels, is the largest brain barrier in terms of length, (close to 650 km) and surface (10–20 m^2). It protects the brain from exogenous and circulating threats and maintains brain homeostasis (Saint-Pol et al., 2020). Despite its size, various neuroinvasive viral pathogens, such as rabies, HIV-1, West Nile, Zika, and influenza are able to breach the BBB (Berger & Avison, 2004; Chai et al., 2014; Chaves et al., 2014; Diamond & Klein, 2004; Leda et al., 2019; Marshall, 1988; Mustafa et al., 2019; Paterson, 2005; Resnick et al., 1988; Wang et al., 2013). These viruses negatively affect the barrier by direct interaction with the ECs, as well as by induction of host immune responses that result in elevated expressions of pro-inflammatory chemokines, cytokines, and cell adhesion molecules that lead to a deterioration of the barrier's functional and structural integrity (Dahm et al., 2016). A disruption of the BBB can result in the crossing of viral particles and infected immune cells, which can further elevate the levels of inflammatory mediators (Al-Obaidi et al., 2018; Dahm et al., 2016; Daniels et al., 2014; Spindler & Hsu, 2012). It is therefore possible that SARS-CoV-2 can use these mechanisms of neuroinvasion, and may also primarily enter the CNS by crossing the BBB. Interactions between SARS-CoV-2 and components of the BBB therefore have the potential to significantly impact neuropathogenesis. Further support to the BBB route hypothesis is given by the facts that BBB is disrupted in hypertension (Setiadi et al., 2018) and hypertension is a frequent comorbidity for COVID-19 (Espinosa et al., 2020; Gold et al., 2020; Parveen et al., 2020; Surma et al., 2020; Zaki et al., 2020).

The BBB is a highly restrictive barrier that protects the CNS from aberrant immune responses and pathogens in the periphery. BBB is formed by the brain ECs lining the cerebral microvasculature with about 50–100 times tighter contacts than that in the peripheral microvessels and astrocytes, which are in direct contact with the ECs (Abbott, 2002). Astrocytes play a central role in maintaining homeostasis within the CNS by regulating the integrity of the BBB, as well as by controlling the uptake of excess neurotransmitters and other extracellular factors that may perturb neurotransmission (Abbott, 2002). It was also pointed out that several biomolecules, such as Endothelin-1 (ET-1), Glutamate, IL-1β, IL-2, IL-6, TNFα, macrophage inflammatory proteins MIP-2, and nitric oxide might modulate the BBB permeability, with at least some of these biomolecules being released by astrocytic glial cells (Abbott, 2002).

Notably, a deregulated immune response serves as an important mediator of COVID-19 mortality (Pedersen & Ho, 2020), as critical illnesses are more likely to develop in patients with heightened levels of inflammatory cytokines (Chen, Wu, et al., 2020; Chen, Zhao, et al., 2020; Qin et al., 2020; Tan et al., 2020; Yang, Li, et al., 2020; Yang, Shen, et al., 2020). These conditions are referred to as "cytokine storms" and result in an increase in vascular permeability, which facilitates immune cell efflux into affected tissues, while also possibly worsening pneumonia (Zhang et al., 2020). Importantly, most of the proteins that were shown to modulate the BBB permeability (Abbott, 2002) are part of the cytokine storm in severe COVID-19 cases. One of the outputs of the systemic inflammation is known to cause vascular injury, including breakdown of collagen and permeability of BBB. For example, influenza A virus infection disturbs BBB via the systemic elevation of the levels of the matrix metallopeptidase 9 (MMP-9) (Muhammad et al., 2011, 2016; Takahashi et al., 2018), which is a member of the family of zinc-metalloproteinases involved in the degradation of the extracellular matrix and which breaks collagen present in the basal membrane of every arterial wall, thereby leading to a high collagen turnover in systemic circulation (Hackenberg et al., 2020) and to the increase in BBB permeability. Such BBB permeability elevation represents a link between MMPs (specifically MMP-9) and CNS disorder (Bongetta et al., 2020; Wu et al., 2020).

Under physiologic conditions, the BBB is relatively impermeable, though recently the list of biomolecules capable of modulating the permeability, integrity, and tightness of the BBB was extended by inclusion of the SARS-CoV-2 spike protein (Buzhdygan et al., 2020). It was shown here that introduction of the viral spike proteins into the model systems recapitulating the essential features of the BBB resulted in a breach of the barrier. Furthermore, SARS-CoV-2 spike

protein was shown to increase the *MMP3*, *CCL5*, *CXCL10*, *ICAM-1*, and *VCAM-1* (which are cell adhesion molecules, CAMs) gene expression levels, alter mRNA levels of interleukins IL-1β and IL-6, and trigger a pro-inflammatory response on brain ECs that may further contribute to an altered state of BBB function (Buzhdygan et al., 2020). These observations were used to support a hypothesis that SARS-CoV-2 is potentially a neuroinvasive virus since it can turn on the machinery to enable the migration of infected immune cells into the brain parenchyma (Buzhdygan et al., 2020). In blood vessels, the increase in *VCAM1 and ICAM1* in response to the pro-inflammatory cytokines plays a crucial role in the adhesion of leukocytes, including macrophages and neutrophils, with the end result being disruption of the BBB and inflammation of the brain (Choi et al., 2020). Viral gene products can also contribute to the BBB breakdown through upregulation of many biomarkers (Swanson & McGavern, 2015). *CXCL8*, *CXCL10*, *CXCL13*, *VCAM-1*, *MMP2*, *MMP14*, and *IL-6* were shown to be overexpressed in COVID-19 patients (Ackermann et al., 2020). All of these molecules were demonstrated to increase the permeability of the endothelial/epithelial cell barriers (especially in nervous system) or decrease its electric resistance and/or cleave the tight junction proteins and promote leukocyte extravasation from the blood (reviewed in detail in (Swanson & McGavern, 2015)).

Therefore, SARS-CoV-2 is able to breach the BBB during the course of ongoing infection. Then, similar to the earlier observations for SARS-CoV (Channappanavar & Perlman, 2017), interactions of SARS-CoV-2 S protein with ACE2 in multiple brain regions allows the virus to infect the brain. More severe cases of COVID-19 may result in higher probabilities of BBB disruption, which can be associated with strong immunologic responses, such as the cytokine storm pathologies or some co-infection, or other comorbidities.

Therefore, viruses might invade the CNS by entering through the ECs of the BBB and the blood–CSF barrier in the CP. Studies conducted by Bulfamante et al. (2020) and Paniz-Mondolfi et al. (2020) strongly support this hypothesis. The authors captured the viral particles using a cytoplasmic vacuole at the endothelial neural cell interface in a transmission electron microscope (TEM), suggesting that SARS-CoV-2 is able to bind to vascular endothelium, penetrate the BBB, and invade nervous tissues through hematogeneous pathways.

The presence of SARS-CoV-2 in the brain was demonstrated by TEM analysis of the sections obtained at postmortem that revealed the presence of 80 to 110 nm viral particles in frontal lobe brain sections (Paniz-Mondolfi et al., 2020). The presence of the virus there was further confirmed by testing the frozen front lobe tissue via running in parallel brain samples in four RT-PCR assays that targeted different regions of the viral genome, *ORF1/a* and *E* genes, *N1*, *N2*, *N3*, *N2* and *E* genes, and *ORF1ab* and *S* genes. SARS-CoV-2 was detected in the brain tissue, while the RT-PCR testing did not detect SARS-CoV-2 in a postmortem CSF samples (Paniz-Mondolfi et al., 2020). However, other reports detected SARS-CoV-2 in the CSF samples of the COVID-19 patients from three different countries (USA, Brazil, and Japan).

In the first report, PCR detected the SARS-CoV-2 in the CSF of a 40-year-old Los Angeles resident with type 2 diabetes mellitus and obesity, who developed fever and temporary loss of consciousness (syncope) and was admitted for encephalitis (Duong et al., 2020; Huang et al., 2020). In the second report, the SARS-CoV-2 genome was detected and sequenced in a 42-year-old resident of São Paulo with suspected demyelinating disease (Domingues et al., 2020). In the third report, RT-PCR analysis detected SARS-CoV-2 in the CSF of a Japanese patient with meningitis/encephalitis associated with SARS-CoV-2 (Moriguchi et al., 2020). Although SARS-CoV-2 RNA was found in the CSF, no reports have detected and/or demonstrated the presence of the viral particles in the CSF of COVID-19 patients. Therefore, the RT-PCR positivity of the CSF samples for the SARS-CoV-2 RNA does not necessarily imply the presence of the entire infectious viral particles in there, as clearly demonstrated by the inability to detect the full-genome consensus in the CSF samples, where only 1,580 nucleotides of two fragments from ORF1a were sequenced (Domingues et al., 2020). Despite all this, the data collected so far support the BBB breach as an important SARS-CoV-2 entry route. Furthermore, it is possible that the SARS CoV-2 infection could be more persistent in the CNS, which is clearly an immunoprivileged site (Domingues et al., 2020). Another possibility for the SARS-CoV-2 to cross the BBB and pass into the CNS is via the infection of the blood cells capable of BBB crossing (Zubair et al., 2020).

Observation of the virus-like particles in blood vessel ECs of BBB may point to a hematogeneous route of entry of the virus into the nervous system (Paniz-Mondolfi et al., 2020). Neuronal retrograde and hematogeneous routes were considered for the entry of neurotropic respiratory viruses into the CNS (Desforges et al., 2019). In the hematogeneous route, viruses gain access to the CNS by using inflammatory cells as "Trojan horses," or by infecting ECs of the BBB or epithelial cells of the BCSFB in the CP (Desforges et al., 2019). In the neuronal retrograde route, viruses undergo retrograde axonal transport to reach the neuron cell bodies in the peripheral and or CNS (Desforges et al., 2019). For example, analysis of the MERS-CoV tissue pantropism (i.e., the ability of a virus to indiscriminately affect many kinds of tissues) has shown that MERS-CoV can enter the bloodstream after endothelial infection *in vivo* (Hocke et al., 2013). This hypothesis is further supported by the presence of SARS-CoV-2 in the CSF fluid of a COVID-19 patient presenting viral encephalitis (Vonck et al., 2020; Zhou et al., 2020).

11.2 | The blood–nerve barrier

The mammalian BNB is the second most restrictive vascular system after the BBB (Ubogu, 2020). Peripheral nerves are structurally divided into three compartments: *epineurium*, where fenestrated macrovessels directly derived from the extrinsic peripheral nerve blood supply are located; the inner *perineurium*, which surround the *innermost endoneurium* compartment of the peripheral nerve. The BNB, formed by the tight junction-forming microvessels within peripheral nerve endoneurium, allows for effective axonal signal transduction.

The restricted permeability of this barrier protects the endoneurial microenvironment from drastic concentration changes in the vascular and other extracellular spaces. This barrier supplies cover to the nerves everywhere in human body, constitutes the ECs, and is characterized by very compact structure (Figure 2d1,d2). The analysis of its transcriptome provided insights into the mechanisms of microbial entry from the bloodstream into peripheral nerves, human BNB response to injury, and response to viral infections.

Inflammatory and metabolic diseases, as well as traumatic lesions of the nervous system, are accompanied by BNB/BDB (blood dorsal ganglion barrier) opening. Opening of the BNB (or permeable/leaky BNB) can be the first sign preceding neuropathic pain, which synchronizes with many agents, such as cytokines, growth factors, and microRNAs (Reinhold & Rittner, 2020). Because ECs forming the BNB are the only cells that come into direct contact with the blood constituents in the PNS, ECs can be easily manipulated via system circulation, or indirectly via pericytic activity, including release of various cytokines and chemokines that influence endothelial function (Ubogu, 2020). The BNB ECs could transport the IgG, RNA, chemokine, hormones, and delivery drugs while the large molecular weight antibody subclasses (sIgM and sIgA) do not undergo human BNB transport under standard physiological condition, which may modulate in pathophysiological conditions. BNB ECs respond to physiological cytokine/chemokine stimulus and normal/pathologic leukocyte trafficking across the BNB (Palladino et al., 2017).

Some neurotropic viruses have been found to be able to hijack the peripheral nerve barrier, such as herpes simplex virus and swine hemagglutinating encephalomyelitis virus (HEV) (Li et al., 2012, 2013; Matsuda et al., 2004). Although there are no data concerning SARS-CoV-2 trafficking across the BNB, some observations concerning the barrier permeability may point to the ability of SARS-CoV-2, or at least its proteins, to target the BNB and to modulate its peripheral nerve immunosurveillance in COVID-19 pathogenesis. In fact, several disorders, such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy, acute inflammatory demyelinating polyradiculoneuropathy, and vasculitic neuropathy are characterized by hematogeneous leukocyte infiltration (predominantly monocytes and T cells) into peripheral nerves via the BNB, with resultant demyelination and axonal degeneration (Ahmad & Rathore, 2020; Chen, Wu, et al., 2020; Conde Cardona et al., 2020; Lai et al., 2020; Mao et al., 2020; Vonck et al., 2020; Zubair et al., 2020). Therefore, it seems that leukocyte extravasation alone can impact junctional protein expression in the BNB. The chemokine-mediated and/or hyperproduction of interleukin-6 signaling has been implicated in the autoimmune neuropathies pathogenesis (Cardona & Ubogu, 2013; van Doorn et al., 2008; Ubogu, 2013). Clinically, GBS is characterized by limb or cranial nerve weakness, loss of deep tendon reflexes, sensory, and dysautonomic symptoms due to peripheral nerves and root demyelination, and/or axonal damage. About 60% of all GBS are preceded by respiratory or GI complications, with a presentation latency varying from 3 days to 6 weeks (van Doorn et al., 2008), which corresponds with COVID-19 GBS patients (Agosti et al., 2020). The suggested infection-mediated immune response that results in higher circulation of pro-inflammatory cytokines (Agosti et al., 2020; Ahmad & Rathore, 2020; van Doorn et al., 2008) reaches the peripheral nerve through the BNB.

Finally, the GBS and other peripheral nerve symptoms reveal that the PNS can be hijacked by SARS-CoV-2 through direct attack of microvessel ECs, or indirect attack via immune-mediated response. As ACE2 is widely expressed on the epithelial cells of the oral mucosa, SARS-CoV-2 can breach the BNB accessing the CNS via the cranial nerve using axonal transport machinery (Zhou et al., 2020). The upregulated vascular endothelial growth factor VEGF (C and A) is associated with COVID-19 endothelial barrier dysfunction (Ackermann et al., 2020; Yin et al., 2020), and specifically with the BNB (Lim et al., 2014). As VEGF is also related to angiopoietins (Ang I and Ang II), accumulation of Ang II facilitates the elevation of VEGF and inversely augments Ang II, which forms a vicious cycle in the release of inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-8, and ICAM-1, which causes BBB and BNSB disruption (Yin et al., 2020).

11.3 | Blood–cerebrospinal fluid barrier

The CP of the BCSFB displays fundamentally different properties in comparison to the BBB. With a brisk blood flow (10 times higher than that of the brain) and highly permeable capillaries, the human CP provides the CNS with a high turnover rate of fluid (~400 ml/day) that contains peptides, micronutrients, and hormones for neuronal networks. BCSFB cells are the CP epithelium cells that line the cerebral ventricles and the arachnoid epithelium that line the brain vasculature in the subarachnoid space (Abdul Razzak et al., 2019). CP epithelial is considered to be less electrically resistant compared to the BBB endothelial, and is somewhat "leaky." Therefore, it is the prime target for viral entry into the CNS. Tight junctions (TJs) allow for EC occlusion and strict permeability by sealing off the intercellular space between the ECs lining the microvessel. TJs (e.g., occludins, claudins, and junctional adhesion molecules) are transmembrane proteins that bind intracellularly to the actin component of the filamentous cytoskeleton and extracellularly to identical transmembrane proteins in adjacent ECs (Abdul Razzak et al., 2019).

As discussed under the BBB route, the SARS-CoV-2 particle could not be isolated and/or detected in the CSF, although the RT-PCR was positive and two fragments from ORF1a of the 1,580-nucleotide were obtained (Domingues et al., 2020; Moriguchi et al., 2020), the CSF of those patients showed an albuminocytologic dissociation with increased protein level (98 mg/dl, reference value: 8–43 mg/dl) and normal cell count (2×10^6/L, reference value: 0–8×10^6/L) (Agosti et al., 2020; Dalakas, 2020; Ellul et al., 2020). Eleven COVID-19–GBS patients from Wuhan, Italy, Spain, and France were analyzed. Although they all had very high concentrations of protein in CSF, in seven of 11 tested patients, the virus was not detected in the CSF, suggesting that there is no direct root of intrathecal viral replication or infection. However, as intravenous immune globulin helped improve the condition of several patients, and one patient exhibited the presence of antibodies to the ganglioside GD1b, it

appears that a post-viral-triggered immune response similar to other post-viral-induced GBS cases or other post-viral autoimmune neurologic disorders occurred (Dalakas, 2020). As SARS-CoV-2 spike protein interacts with ganglioside dimers and the GalNAc residue of GM1 for anchoring to cell surface gangliosides, cross-reactivity between epitopes within the SARS-CoV-2 spike-bearing gangliosides and signature sugar residues of surface peripheral nerve glycolipids is very likely. Similar molecular mimicry has been shown between peripheral nerve glycolipids and Campylobacter jejuni or Zika virus (Dalakas, 2020). This raised many questions, such as how does this SARS-CoV-2 genomic material reach the CSF? Is it through the BCSFB? Is it accompanied by the delivery of the translated SARS-CoV-2 proteins? Are the increased CSF protein concentration and cell counts in COVID-19 linked with BCSFB and BNB permeability as immune-mediated responses?

12 | LYMPHATIC BRAIN DRAINAGE ROUTE

A third way SARS-CoV-2 can enter the CNS could be via the spreading of the virus in the lymphatic drainage system of the brain (Bostanciklioglu, 2020). Although the glymphatic vessel structure mainly contains endothelial lining cell systems, this pathway is rather contradictory at the moment, and other researchers do not confirm lymphatic draining entry (Li, Guan, et al., 2020). The lymphatic/glymphatic brain system (which is a glial-dependent waste clearance pathway in the brain that serves as a "front end" for the waste clearance connected downstream to an authentic lymphatic network) was discovered rather recently (Benveniste et al., 2019). It has a vascular histological structure, which is quite similar to that of the endovascular blood system (Aspelund et al., 2015; Da Mesquita et al., 2018). Importantly, endothelial lining cells of this system express both the *ACE2* and *TPMRSS2* genes, where the SARS-CoV-2 can access it. In line with these features, electron microscopy analysis revealed the presence of viral inclusion structures in ECs (Varga et al., 2020b). The lymphatic/glymphatic system is different from traditional blood circulation since it is an open, afferent (one-way) system. The major function of this system is to collect the soluble waste proteins and metabolic products from the CNS and drain them away. This unidirectionality raises an important and logical question, namely, how can it bring the viral particles to the CNS tissue, being a one-way drainage system? In addition, the lymphatic drainage function is impaired in age-dependent manner (Da Mesquita et al., 2018).

Therefore, the aforementioned BBB route is more favorable for CNS infection by SARS-CoV-2, especially in patients with severe COVID-19 complicated with the cytokine storm, which increases the BBB permeability, thereby facilitating the immune cell efflux into the affected tissues. At least in the severe cases, the virus (free or in vacuoles) is disseminated into many organs including the vasculature system, and can cause endothelilitis by attacking the endothelium. This may explain the frequently observed prothrombotic state with *in situ* clot formation and the impaired microcirculatory function across different organs in COVID-19 patients. Based on these observations, it was suggested that one of the approaches to affect the course of COVID-19 would be to take some steps to stabilize the endothelium during viral replication, specifically in vulnerable patients with preexisting endothelial dysfunctions, which are commonly associated with the male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all being linked to adverse outcomes in COVID-19 (Varga et al., 2020b).

13 | PERIPHERAL NERVE OR NEURONAL RETROGRADE ROUTE: ACCESSING CNS VIA ENTERIC, LUNGS, AND KIDNEY NERVES ROUTES

Although the direct neuroinvasion via hematogeneous spread or migration of SARS-CoV-2 through the olfactory tract are possible infection routes to the CNS (Wu et al., 2020; Wu & McGoogan, 2020), the virus could also gain access from the periphery (Esposito et al., 2020). It has been postulated that brain stem invasion may occur via the vagal afferents from the upper airways, lung, and GI (Esposito et al., 2020; Li, Bai, et al., 2020). Furthermore, one cannot exclude the role of GI tract involvement (a notion giving some tribute to the prospective gut-brain connection). In fact, the GI represents an important but mostly underestimated niche for SARS-CoV-2 replication. This is because the GI epithelium has higher relative expression of ACE2 receptor than the lungs. Furthermore, SARS-CoV-2 can directly infect the intestinal cells and efficiently replicate there. Finally, it was pointed out that the clinical outcome was worse for COVID-19 patients with concomitant GI symptoms who required mechanical ventilation due to increased acute respiratory distress (Jin et al., 2020). One study suggests that SARS-CoV-2–related diarrhea and the GI dysfunction are not merely accessory symptoms, but serve as a possible marker of the involvement of the enteric nervous system/enteric glial cell (ENS/EGC) in pathogenesis, and suggests an alternative pathophysiological mechanism underlying SARS-CoV-2 neuroinvasion (Esposito et al., 2020). Here, the gut might serve as the "entrance door," by which viruses may either directly neuroinvade or indirectly immunologically prime the ENS or ascend to the CNS through intestinal vagal afferents (Esposito et al., 2020). This hypothesis is supported by the fact that there is a strict interconnection between the ENS and the EGCs and that the gut epithelium is part of a neuroepithelial unit crucial for gut homeostasis (Esposito et al., 2020).

It was also established that in the case of MERS-CoV infection, the enteric involvement could take place before the respiratory infection (Zhou et al., 2017). Furthermore, brain infection was observed in mice infected with MERS-CoV either intranasally or by intragastric inoculation (Zhou et al., 2017). Although finding brain infection in mice with intranasal MERS-CoV injection is not surprising and was actually expected, the fact that mice that underwent intragastric inoculation with MERS-CoV showed infectious virions in both brain and lung homogenates 5 days after the inoculation was

rather surprising (Zhou et al., 2017). The retrograde axonal transport and transsynaptic transfer are well-documented for other types of coronavirus such as the avian bronchitis virus and the swine HEV (Li et al., 2013; Matsuda et al., 2004).

EGCs express the major histocompatibility complex class II and functionally work as antigen-presenting cells for both innate and adoptive immune cells localized in the gut-associated lymphoid tissue (GALT) (Lee et al., 2020). GALT houses many types of immune cells, such as T lymphocytes (γδ T lymphocytes). Upon activation by viral infection, GALT could initiate many immunological responses, such as transition of native $CD4^+$ lymphocytes into different subtypes (T_h1, T_h2, T_h17, T_{reg}, T_{sup}, and $CD8^+$). Furthermore, an enormous release of IL-6 and other inflammatory mediators also occurs upon activation, contributing to the acute respiratory distress as observed in the COVID-19-induced cytokine storm (Esposito et al., 2020; Mehta et al., 2020) and to the increase in the endothelium permeability, as aforementioned.

It was shown that the susceptibility to the SARS-CoV-2–inflicted GI damage of the inflammatory bowel disease (IBD) patients is determined by the dysregulated mucosal *ACE2* and *TMPRSS2* expression in the colon and ileum in IBD (Krzysztof et al., 2020). This deregulation was further enhanced by advanced age, smoking, and active disease that served as potential additional risk factors defining the vulnerability of IBD patients to COVID-19 through alterations in receptor expression (Krzysztof et al., 2020).

Furthermore, it was established that both SARS-CoV and SARS-CoV-2 can efficiently infect enterocyte linage cells in human small intestinal organoids (hSIOs, which are the 3D structures that are grown from adult stem cells (ASCs) and recapitulate key aspects of the organ from which the ASCs were derived) (Lamers et al., 2020). This efficient infection of enterocytes in hSIOs by SARS-CoV and SARS-CoV-2 was demonstrated by confocal- and electron-microscopy, since the clusters of the extracellular viral particles (80–120 nm) were detected in the lumen of organoid and in the apical side of enterocytes associated with double membrane vesicles (Lamers et al., 2020). Could the viral particles of these disintegrated-infected cells somehow reach and infect the glial intestinal cells, which are known to express ACE2 and TMPRSS2/furin? Could this scenario be repeated in other organs such as the heart, lungs, kidney, and even cutaneous tissues? Similar to SARS-CoV and SARS-CoV-2 infecting the human intestinal epithelial organoid (Lamers et al., 2020), SARS-CoV-2 was shown to directly infect engineered human blood vessel organoids *in vitro* (Monteil et al., 2020). Using both immunochemistry and electron microscopy, SARS-CoV-2 viral particles were found in skin endothelium of patients presenting with chilblains (the painful inflammation of small blood vessels in the skin) (Colmenero et al., 2020). As SARS-CoV-2 multiplies in the vascular cells of the skin area, can it go through the blood withdrawn by a mosquito bite? Ultrastructural examination identified typical CoV particles characterized by the spike structure in cytoplasm of hepatocytes in two COVID-19 cases (Wang, Liu, et al. 2020). Also, SARS-CoV-2 particles were found in heart, kidney, and lung autopsy of postmortem samples (Pesaresi et al., 2020). Therefore, SARS-CoV-2 may first infect blood vessels' ECs prior to infection of local tissues (Monteil et al., 2020), and then be disseminated into many organs, including the human nervous system (Colmenero et al., 2020; Monteil et al., 2020; Varga et al., 2020b).

14 | SOMAL CARGO ROUTES

14.1 | Macrophage/monocytes cargo route

Some viruses are neurotropic, being able to invade nervous tissues and cause infections of immune-functioning macrophages, microglia, or astrocytes in the CNS (Al-Obaidi et al., 2018; Soung & Klein, 2018). Respiratory viruses may enter the CNS via a hematogeneous or a neuronal retrograde route. In the first route, the virus disrupts the nasal epithelium and reaches the bloodstream and leukocytes, and—by manipulating the innate immune system—invades other tissues, including the CNS. Furthermore, in this route, leukocytes may act as a reservoir for viral transmission for neuroinvasive CoVs (Desforges et al., 2019). In the second route, the virus could infect peripheral neurons and access the CNS through retrograde transsynaptic neuronal dissemination (Desforges et al., 2019). It is known that both alveolar and interstitial macrophages in the lungs express the ACE2 receptor and the TMPRSS2/Furin proteases, as well as ADAM-17, which acts as sheddase of ACE2. In the presence of all components of viral activation and binding, the virus can replicate in human macrophages (Abassi et al., 2020) and dendritic cells (Yang, Chu, et al., 2020), but the mature viral particles could not detected intra or extracellular from both of cells type. Furthermore, the electron microscopic postmortem examination of the lung tissues clearly showed that the SARS-CoV particles and SARS-CoV-2 antigens are present and distributed in both alveolar macrophages, as well as in the lymph nodes and the spleen (Chen, Feng, et al., 2020; Shieh et al., 2005). Previous data from 15 autopsies indicated that the SARS viral particles and genomic sequences were detected in a large number of circulating monocytes, lymphocytes, and lymphoid tissues. They were also found in the mucosa of the intestine, the epithelial cells of the respiratory tract, the neurons of the brain, the epithelium of the renal distal tubules, and macrophages in different organs, suggesting that the virus could infect multiple cell types in different organs (Gu et al., 2005). One interesting find was that a large proportion of lymphocytes in the circulation and lymphoid organs contained the virus, as observed in the TEM image of a circulating T lymphocyte in a patient who had SARS 6 days after onset of a fever, which may indicate that these circulating lymphocytes carrying viral molecules could reach the CNS and PNS via BBB, BCSFB, or BNB, or through all of these barriers. Based on this interesting result the mechanism of SARS pathogenesis was postulated (Gu et al., 2005), which appeared to be working until today. It is likely that the viral infection may convert these cells into long living macrophages (Mφ) and promote their migration into extrapulmonary organ/tissues, where they become infected resident cells (viral reservoir) and as inflammatory signals producer, serve as a Trojan horse in other organs (Abassi

et al., 2020), with others cell types such as leukocytes, ECs, smooth muscle cells, pericytes, inflammatory cells, neurones, or glial cells (Jaunmuktane et al., 2020). A CD68 immunostain revealed that the macrophage infiltrated the cerebral hemispheres and subcortical white matter lesion associated with an axonal injury, and a perivascular acute disseminated encephalomyelitis (ADEM)-like appearance (Jaunmuktane et al., 2020; Reichard et al., 2020).

14.2 | Double membrane vesicles cargo route

Many viruses have been shown to enter the extracellular double-membrane vesicle (EDMV) or exosome avenues during intrahost spreading and synthesis (Badierah et al., 2020). As previously reviewed in detail, all positive-sense single-stranded RNA viruses (including SARS-CoV and MERS-CoV) use, redirect, and rearrange host cell membranes as part of the viral genome transcription and replication tactic, harnessing their nonstructural protein apparatus nsp1-16 (Elrashdy et al., 2020). This tactic allows them to produce double-membrane vesicles of different size and configuration, carrying different levels of viral particle structures, from dsRNA to full mature viral particles, which would be released as EDMV or exosomes during the release from the host cells, or as a result of the post cell-host rapture. SARS-CoV-2 seems to be using a similar avenue of replication and release. This conclusion is based on the careful postmortem histopathological electron microscopy analysis, and further confirmed using the *in vitro* SARS-CoV-2 cultured on Vero E6 cells (Ogando et al., 2020). In fact, electron microscopy revealed that the ultrastructural changes induced by both SARS-CoV and SARS-CoV-2 are very similar and take place at comparable times after infection. However, the important differences between the two viruses were the facts that, (a) SARS-CoV-2 generated higher levels of intracellular viral RNA, but 50-fold less infectious viral progeny was recovered from the culture medium, (b) upon passaging in Vero E6 cells, SARS-CoV-2 was apparently under strong selection pressure to acquire adaptive mutations in its spike protein gene (Ogando et al., 2020). These mutations changed or deleted a putative furin-like cleavage site in the region connecting the S1 and S2 domains of the S-protein and resulted in a very prominent phenotypic change in plaque assays (Ogando et al., 2020).

Of note, SARS-CoV-2 could infect almost all human body organs and tissues (Ackermann et al., 2020; Colmenero et al., 2020; Elrashdy et al., 2020). The infected cells are shedding the exosomes (EDMVs). Furthermore, apoptotic or the diffuse damage of infected cells can lead to the release of their contents in a form of different types of EDMVs containing different viral structures (ranging from viral dsRNA to mature viral particles), to infected the adjacent new cells/tissues and expanded to circulate systemically and disseminate to reaching distant tissues (Elrashdy et al., 2020). This hypothesis is supported by Bulfamante et al., 2020; Colmenero et al., 2020; Paniz-Mondolfi et al., 2020, where viral particles were detected in ECs of lungs, kidneys, skin chilblains, and CNS of vascular system and organs-cross talk via the vascular system. The TEM analysis of the postmortem frontal lobe brain sections showed the presence of viral particles. Pleomorphic spherical viral-like particles having variation in the size and shape were found either individually or within the small vesicles of ECs. The possible active pathogen transcellular penetration (entry-transit process) across the brain microvascular ECs into the neural niche was evidenced as blebbing of viral-like particles coming in/out of the EC wall. Neural cell bodies exhibited distended cytoplasmic vacuoles containing enveloped viral particle exhibiting electron dense centers with distinct envelope projections ending in round "peplomeric" structures typical of a coronavirus particle (Paniz-Mondolfi et al., 2020). In the light of these findings, it seems logical that the virus can access the brain directly through the permanent destabilization of the BBB, specifically in patients with very severe viral infection complications accompanied by systemic inflammatory responses, in its free form or vacuolated in double membrane vesicles. In turn, not only viral particles but the peripheral cytokines can gain entry to the CNS, and consequently exacerbate or trigger neuroinflammation that can result in many neurological manifestations, including encephalitis (De Felice et al., 2020).

The isolated EVs released from DENV-2 infected U937 macrophage cell line carrying the viral NS3 protein and different miRs induced an increase in the polarization of the endothelial (EA.hy926) monolayer cells permeability, as well as changes in the expression of ICAM and the VE-cadherin, also leading to an increase in the levels of the IP-10, TNF-α, RANTES, IL-10, and MCP-1 secretion, even in the absence of the virus (Velandia-Romero et al., 2020), suggesting that a pro-inflammatory status was involved in the endothelial permeability alteration. The miRs most frequently counted within the vesicles obtained from such DENV-infected cells include the miR 21, miR 92a, and miR 191, which are strongly associated with many biological pathways involving EC processes, such as tubular network formation, angiogenesis, and brain microvascular reparation. Such vesicles obtained from the DENV-infected cells induced an endothelial activation, possibly determined by the miR that they contain (Velandia-Romero et al., 2020).

Different cultured glial cell types released the EDMVs, as well as EDMVs of different sizes were detected in CSF. EDMVs are able to cross the BBB in both directions, though it is unclear what the route of transfer is. Also, the peripheral EDMVs can interact with the BBB leading to changes in the barrier's properties. EDMVs can enter the brain parenchyma at the CP and to facilitate folate import into the brain. Of note, the inflammatory conditions often associated with a leaky BBB facilitated the entry of peripheral EDMVs into the brain, resulting in genetic modulation of the target cells of the CNS. These results indicate to that the EDMVs may act as a means of the nonsynaptic neuronal cell communication, hence the EDMVs released from neurons are likely involved in the transfer of biomolecules across synapses. Furthermore, all types of macroglia and microglia (phagocytic cells) contributing to CNS tissue homeostasis can secrete EDMVs in the form of exosomes or microvesicles (reviewed in (Basso & Bonetto, 2016; Saint-Pol et al., 2020; Yanez-Mo et al., 2015)).

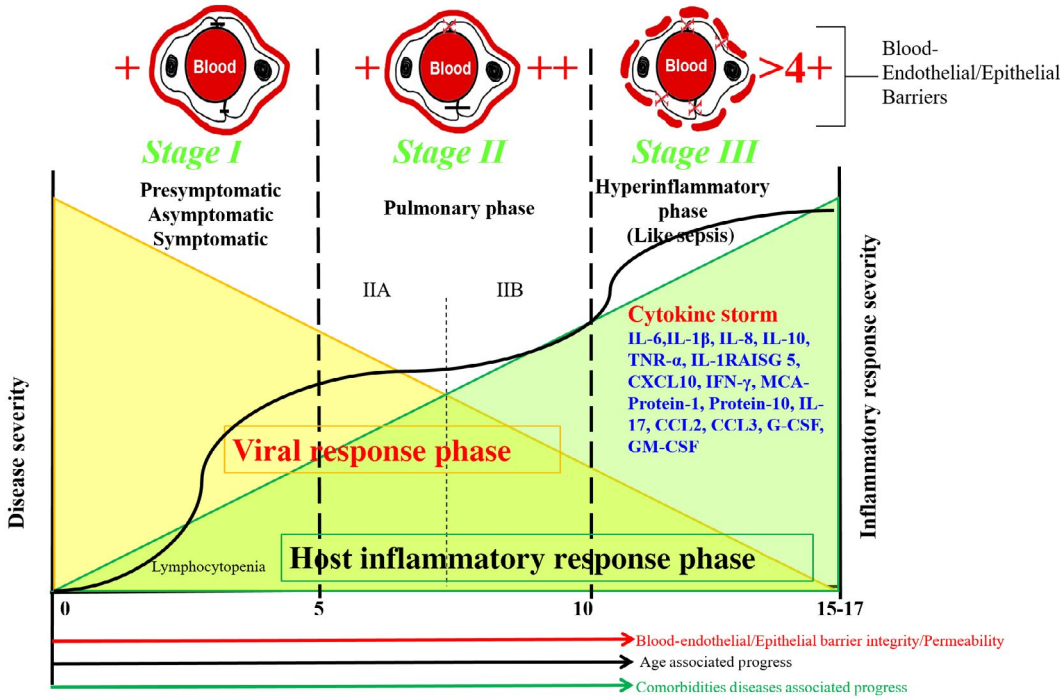

FIGURE 3 Classification of COVID-19 disease stages. The figure illustrates three escalating phases of COVID-19 disease progression, with hypothesis of blood–endothelial/epithelial barriers integrity/permeability scale associated with age and comorbidities diseases over the three stages. The blood–endothelial barriers are representative for all body barriers and specifically for blood–nervous system barrier (BNSB). Progressive increase in inflammatory cytokine and chemokines eventually leads to cytokine storm in a profile similar to in sepsis cases, which eventually leads to endothelial barrier dysfunction. Many other biomarkers molecules (in addition to the cytokine storm elements) have a direct effect on the BNSB as discussed in text. The times on the x axis are approximate. The figure designed based on and adapted from (Akhmerov & Marban, 2020; Delaney & Campbell, 2017; Doran et al., 2013; Elrashdy et al., 2020; Li, Liu, et al., 2020; Siddiqi & Mehra, 2020). + to >4+ indicative for barrier integrity/permeability like scale, IIA (stage II without hypoxia) IIB (Stage II with hypoxia). Tumor necrosis factor (TNF-α), interleukin 1β (IL-1β), IL-6, GCSF: granulocyte-colony stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, and MCA-protein 1: macrophage inflammatory proteins 1-α [Color figure can be viewed at wileyonlinelibrary.com]

14.3 | COVID-19 brain access via nicotinic acetylcholine receptor (nAChR)

It is known that there are functional connections between the ACE2 expression and nicotine exposur

e in lungs and other organ systems, such as the kidneys and heart. It is likely that because of these functional connections and due to the capability of nicotine to interact with the components of other renin angiotensin system, smoking can promote COVID-19 cellular entry through the nAChR signaling pathway. Notably, nAChRs are found on the surfaces of many of the same cells that express ACE2 in the kidneys, lungs, circulation, and in the brain, and immune cells (Changeux, 2010; Nordman, Muldoon, et al., 2014; Nordman, Phillips, et al., 2014; Tolu et al., 2013). Therefore, smoking can impact COVID-19 pathophysiology and have a clinical outcome in several organ systems (Kabbani & Olds, 2020). As ACE2 is expressed in the brain and functionally interacts with nAChRs (Ferrari et al., 2007, 2008; Oakes et al., 2018), it was hypothesized that if neural cells, such as epithelial cells, are more vulnerable to infection in smokers since nicotine stimulation of the nAChR can increase ACE2 expression within them (Olds & Kabbani, 2020). This is an important point since it was shown that mRNA from the closely related SARS-CoV, which also binds ACE2 as a mechanism of cell entry, can be detected in brain and CSF of infected individuals (Chong et al., 2004; Inoue et al., 2007; Zhang et al., 2003). Furthermore, SARS-CoV's ability to enter neurons was established in the experimental systems using recombinant human ACE2 as the point of entry (Kaparianos & Argyropoulou, 2011; Netland et al., 2008). Considering this scenario, Olds and Kabbani (Kabbani & Olds, 2020; Olds & Kabbani, 2020) asked important questions, such as: can the COVID-19 infection lead to long-term neural damage in both symptomatic and asymptomatic individuals? And if it can, then can the chronic nicotine exposure through smoking habits and addiction increase the risk of the developing of COVID-19-associated neuropathology through interactions between nAChRs and ACE2 in neurons and glia? These important questions still wait for their answers.

15 | IMMUNE-MEDIATED RESPONSES AND SARS-CoV-2 NEUROLOGICAL COMPLICATIONS

Figure 3 represents three escalating phases of COVID-19 disease progression. Increased vascular permeability is also a hallmark change that occurs in the process of a cytokine storm (Ye

et al., 2020). Although it is known that the cytokine storm (hypercytokinemia) has devastating effects on the respiratory system promoting hyperinflammation and acute respiratory distress syndrome (ARDS), and serves as one of the major causes of the fatal outcomes of the disease, the neurological effects of the cytokine storm are less understood. For example, it is not clear if acute or subacute CNS involvement can be caused by the cytokine storm occurring during the final stage of the disease. A case was reported, where a COVID-19 patient developed acute necrotizing hemorrhagic encephalopathy after several days with altered mental status, cough, and fever (Poyiadji et al., 2020). Although at this stage, the patient demonstrated BBB disruption and the intracranial cytokine storm, no direct viral invasion of the CNS was observed in this case (Poyiadji et al., 2020).

Importantly, the nervous system seems to be affected by the alterations in the neuroinflammatory mechanisms. In fact, immune mechanisms similar to those initiating the cytokine storm in SARS are known to be related to the pathogenesis of multiple neurological diseases, such as cerebrovascular disease, PNS disorders, and postinfectious immune-mediated encephalitis (Serrano-Castro et al., 2020). Furthermore, a pro-inflammatory environment is known to play a role in the pathogenesis and progression of a wide range of neurodegenerative diseases, such as AD, amyotrophic lateral sclerosis, Huntington disease, multiple sclerosis, and PD, where a chronic neuroinflammation causes high levels of cytokines/chemokines (Serrano-Castro et al., 2020). Many of these neurodegenerative diseases are age-related, and the efficiency of the innate immune response is decreased in older age, increasing the vulnerability of these patients to infection (Boe et al., 2017). Older individuals also demonstrate greater severity of the immune response against SARS-CoV-2 infection. All this indicates that there is a potential association of the development and progression of neurodegenerative diseases with SARS-CoV-2 infection that requires careful analysis and better understanding.

Furthermore, although children and adolescents typically demonstrate rather mild COVID-19 course, one cannot exclude the possibility that the SARS-CoV-2 infection may have prospective long-term neurological consequences in these population groups as well, triggering some cognitive and psychiatric disorders. In fact, synaptic pruning during childhood and adolescence can be distorted by the immunological alterations associated with SARS-CoV-2 infection, causing problems that will only become apparent in adulthood (Serrano-Castro et al., 2020).

Both, adaptive and innate immune responses against SARS-CoV-2 infection and virus itself may cause damage within the CNS or PNS. In fact, both ECs of the BBB and epithelial cells of the BCSFB in the CP located in the ventricles of the brain can be targeted by the virus. Furthermore, similar to other viruses (Koyuncu et al., 2013) SARS-CoV-2 can use leukocytes as an intermediate host cell before spreading into CNS from circulatory system (Huang, Zheng, et al., 2020). In fact, such "Trojan horse" mechanism (McGavern & Kang, 2011), where circulating leukocytes are used by viruses to carry them across the BBB, was described for HIV (Kaul et al., 2001), Zika virus (Ayala-Nunez et al., 2019), and HCoV-229E (Collins, 2002; Desforges et al., 2007; Patterson & Macnaughton, 1982). In other words, SARS-CoV-2 is potentially able to establish a reservoir in leukocytes converting them into the delivery vehicles disseminating infection outside the respiratory tracts and spreading it into the other tissues including CNS (Huang, Zheng, et al., 2020).

Transmission electronic microscopy analysis of a brain tissue specimen obtained from the SARS patient succumbed to encephalopathy revealed the presence of SARS-CoV-like viral particle, and a SARS-CoV strain was isolated from this sample, clearly demonstrating the neurotropic potential of this virus (Xu et al., 2005). Furthermore, cytokine/chemokine assay showed elevated expression of a cytokine, monokine induced by interferon-γ (MIG), and interferon-γ–inducible protein 10 in this sample, and the immunohistochemical analysis revealed that a major source for MIG production in the brain was gliocytes (Xu et al., 2005). These findings supported the idea that viral entry to CNS might trigger the infiltration of immune cells and the release of cytokines and chemokines, which contribute to the BBB permeability and/or damage.

Therefore, there is clearly an important interplay between the SARS-CoV-2 and the immune system, where dysfunctional immune responses contributes to the disease progression (Tay et al., 2020). For example, rapid viral replication and secondary cellular injury during the SARS-CoV-2 promoted the increase in the secretion of inflammatory cytokines, such as IL-4, IL-10, IFN-γ, IL-1β, and TNF-α, and the cytokine storm is initiated when the levels of released cytokines are injurious to host cells. The presence of a cytokine storm in severe COVID-19 patients is suggested by their high plasma levels of the inflammatory cytokines (Huang, Wang, et al., 2020). The presence of a cytokine storm combined with the elevated D-dimer (which is a fibrin degradation fragment produced when a blood clot gets dissolved in the body, and which, therefore, serves as a reflection of the presence of thrombosis (blood clotting) and/or thrombotic embolism) and ferritins levels were also reported in SARS-CoV-2–infected patients (Mehta et al., 2020; Xu et al., 2020).

Previous studies on sepsis revealed that sepsis-associated cognitive impairment and other neurological symptoms can be triggered by the cytokine storm-induced BBB disruption and resulting neuroinflammation (Nwafor et al., 2019). This clearly indicates that the activation of the immune system is not only protecting the organism, but also is capable of inducing serious harm, thereby representing a double-edged sword. Contributing factors to the harmful side are the overactivation of the immune system, infection-induced cytokine storm, and the increased immunoglobulin levels in CSF (Wang, Shen et al., 2020). In line with these mechanisms, neurologic features in severe SARS-CoV-2 infection were shown to be combined with the elevated IgG levels and the presence of the oligoclonal bands (which are defined as at least two CSF electrophoresis bands seen in the CSF samples with no corresponding band present in the serum) in the CSF (Wang, Shen, et al., 2020). Furthermore, the development of acute necrotizing encephalopathy or GBS in virus-infected patients can be associated with intracranial cytokine storms

leading to the breakdown of the BBB without direct viral invasion of the CNS (Dalakas, 2020). In the classic view, acute lung injury and ARDS represent an inflammatory disruption of the epithelial and endothelial cellular barriers of the alveolar-capillary unit, with ensuing microvascular hyperpermeability and flooding of alveolar spaces (Matthay & Zemans, 2011).

Another illustration of the double-edged sword concept of immune response activation in SARS-CoV-2 infection is given by the complement system, activation of which represents the first response of the host immune system against SARS-CoV-2 infection. However, "everything is good, which is good in moderation," and uncontrolled complement activation can be harmful as well. In fact, the virus infection of the lungs and other organs can cause complement overactivation leading not only to the acute and chronic inflammation, but to the vasculopathy, for example, EC dysfunction, intravascular coagulation, and thrombus formation, thereby contributing to the multiple organ failure and death (Noris et al., 2020). In other words, such uncontrolled complement activation might initiate some terminal pathways accounting for what clinicians and pathologists are observing in COVID-19 patients, that is, "although the lungs are ground zero, the virus reach can extend to many organs, including the heart and blood vessels, kidneys, gut, and brain" (Noris et al., 2020; Wadman et al., 2020). The activation of complement component C3 exacerbates SARS-CoV–associated ARDS (Gralinski et al., 2018), whereas C3-C5 complement deposits are abundant in the lung biopsies from patients with COVID-19 (Risitano et al., 2020). C5a signaling through its G-protein coupled receptor C5aR1/CD88 increased BBB permeability in neuroinflammatory disease settings *in vivo* (Jacob & Alexander, 2014). It is highly likely that "inflamm-aging" (which is a chronic progressive increase in the pro-inflammatory status associated with the aging process (Franceschi et al., 2000)) is correlated with increased risk of a cytokine storm in some critical elderly patients with COVID-19 infection (Meftahi et al., 2020).

16 | CONCLUSIONS

There are numerous pathways that can be utilized by SARS-CoV-2 to breach the body's defenses reach the PNS and CNS. SARS-CoV-2 or its components reach the nervous system through direct contact specifically in severe COVID-19 cases, or indirect contact through multiple mechanisms of immune-mediated responses in mild-to-moderate COVID-19 cases. We are discussing here that there are at least seven candidate routes, which the mature or immature SARS-CoV-2 components could use to reach the CNS and PNS, utilizing the within-body cross talk between organs. Obviously, utilization of any one of these routes is sufficient to make SARS-CoV-2 neurotropic.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

CONFLICT OF INTEREST

The authors declare that there are no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, E.M.R. and V.N.U.; *Data Curation*, F.E., E.M.R., A.A., S.M.A., R.H.K., and V.N.U.; *Formal Analysis*, F.E., E.M.R., A.A., S.M.A., R.H.K., and V.N.U.; *Investigation*, F.E., E.M.R., A.A., S.M.A., R.H.K., and V.N.U.; *Project Administration*, E.M.R. and V.N.U.; *Supervision*, E.M.R. and V.N.U.; *Validation*, F.E., E.M.R., A.A., S.M.A., R.H.K., and V.N.U.; *Visualization*, V.N.U., E.M.R., R.H.K., and S.M.A.; *Writing – Original Draft*, F.E., E.M.R. A.A., and V.N.U.; *Writing – Review & Editing*, F.E., E.M.R., A.A., S.M.A., R.H.K., and V.N.U. All the authors consented for the final submission.

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