



Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients

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Abstract

Respiratory viruses are opportunistic pathogens that infect the upper respiratory tract in humans and cause severe illnesses, especially in vulnerable populations. Some viruses have neuroinvasive properties and activate the immune response in the brain. These immune events may be neuroprotective or they may cause long-term damage similar to what is seen in some neurodegenerative diseases. The new “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) is one of the Respiratory viruses causing highly acute lethal pneumonia coronavirus disease 2019 (COVID-19) with clinical similarities to those reported in “Severe Acute Respiratory Syndrome Coronavirus”(SARS-CoV) and the “Middle East Respiratory Syndrome Coronavirus”(MERS-CoV) including neurological manifestation. To examine the possible neurological damage induced by SARS-CoV-2, it is necessary to understand the immune reactions to viral infection in the brain, and their short- and long-term consequences. Considering the similarities between SARS-CoV and SARS-CoV-2, which will be discussed, cooperative homological and phylogenetical studies lead us to question if SARS-CoV-2 can have similar neuroinvasive capacities and neuroinflammatory events that may lead to the same short- and long-term neuropathologies that SARS-CoV had shown in human and animal models. To explain the neurological manifestation caused by SARS-CoV-2, we will present a literature review of 765 COVID-19 patients, in which 18% had neurological symptoms and complications, including encephalopathy, encephalitis and cerebrovascular pathologies, acute myelitis, and Guillain-Barré syndrome. Clinical studies describe anosmia or partial loss of the sense of smell as the most frequent symptom in COVID19 patients, suggesting that olfactory dysfunction and the initial ultrarapid immune responses could be a prognostic factor.

Keywords COVID-19 · Human respiratory virus · Human coronavirus · Respiratory viral infection · Neuroinvasion · CNS infection · Acute and chronic neurological diseases · Encephalitis · Encephalopathy

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Introduction

In a review on the central nervous system (CNS) viral infection, Koyuncu et al. concluded that all viruses can reach the CNS under the right conditions depending on viral factors (mutations in specific virulence genes) and host factors (immunodepression, age, and comorbidities) [1]. Respiratory illnesses caused by viral agents, characterized by high rates of morbidity and mortality, are considered problems of critical importance in public health [2–4]. Several human respiratory viruses (including coronavirus CoV) are neuroinvasive and neurotropic with potential neuropathological consequences in vulnerable populations. The neurological manifestation seen in patients with viral infection are caused by what is known as the “cytokine storm” including pro-inflammatory and anti-inflammatory cytokines as an immune reaction to

the viral infection of the CNS. Such an exaggerated response to the infection can lead to meningitis, encephalitis, meningo-encephalitis, or death. The CoVID-19 pandemic, caused by SARS-CoV 2, is a human respiratory virus that causes infection of the respiratory tract and may lead to pneumonia and respiratory failure similar to SARS-CoV, which shows a neuroinvasive and neurotropic capabilities (Fig. 1).

Neuroinvasion, neuroinflammation, and microglia activation

The central nervous system is a highly protected organ from most viral infections by virtue of external multilayer barriers, the blood-brain barrier, and effective immune responses. However, some viruses can still enter the CNS through the hematogenous or neuronal retrograde routes resulting in debilitating direct immune-mediated pathologies, although invasion of the nervous system has no selective advantage for the host or the pathogen. The virus can infect the PNS or CNS either by direct infection of nerve endings in the tissues and using axonal transport machinery to gain access to the CNS (Figs. 2 and 3) [1], or by infecting cells of the circulatory system that ultimately carry the infection through the blood-brain barrier (BBB) into the CNS. In the hematogenous route, several viruses infect endothelial cells of the BBB or epithelial cells in the choroid plexi and therefore invading neuronal tissue by breaking the blood-cerebrospinal fluid barrier or using leukocytes as a vector for dissemination within the CNS [1]. Once the virus escapes these physical barriers and invades the CNS, the first line of defense is the activation of microglia.

Microglia are the residing mononuclear phagocytes of the brain, highly heterogeneous cells within the healthy CNS [5], with multiple morphological and functional profiles depending on their environment. They account for about 10% of the total cell population of the brain [6, 7]. The presence of

activated glial cells is indicative of neuropathology and considered a marker of brain injury and neuroinflammatory events [8]. However, neuroinflammation has been considered a mediator of secondary damage by secretion of cytokines, neurotrophic factors, and activation of proteases for extracellular matrix remodeling. We now know that molecules of the systemic innate immune system or directly impacted neuronal populations can activate the microglia in the brain and start the neuroinflammatory events. While microglia are not the only cells responsible for the inflammatory or immune-mediated responses in the brain, nevertheless, they can rapidly respond to environmental changes. Recently, there is increasing evidence showing that brain resident glial cells can be transformed into an aggressive effector cells causing neuronal damage [9].

Therefore, microglia may confer short-term neuroprotection or trigger long-term neurodegeneration depending on the interplay between pro- and anti-inflammatory cytokines released in response to viral infection.

Viral infection and neuroinflammation are triggers of neurodegenerative diseases

Viruses can lead to brain dysfunction and neuronal damage by direct cytolytic effects or secondary inflammatory reactions (indirect effect) [10]. Neurotropic viruses have developed mechanisms to escape host immune surveillance to gain access to the CNS. The systemic and local inflammatory responses to viruses are potential causes of neuronal damage. Primary infection of neurons leads to acute cell dysfunction that can result in lethal encephalomyelitis [11]. Activated microglia have been considered to be the main contributors to released cytokine and chemokine. However, recently, there is evidence showing that neuronal cells express specific molecules that can play the role of immune receptors to the immune system to modulating the innate immune response in the brain

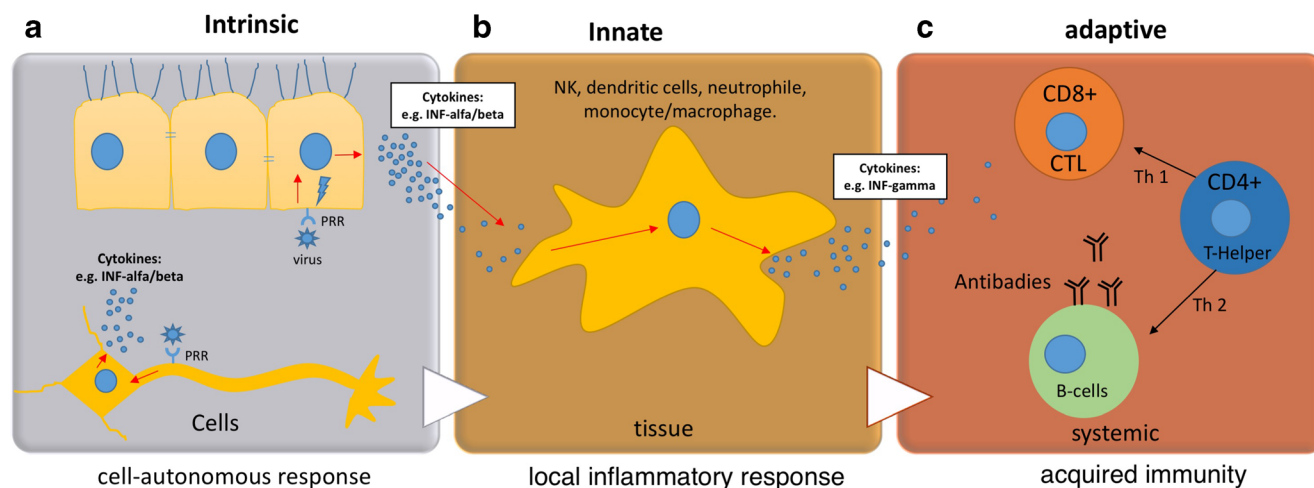


Fig. 1 Immune control of viral infections

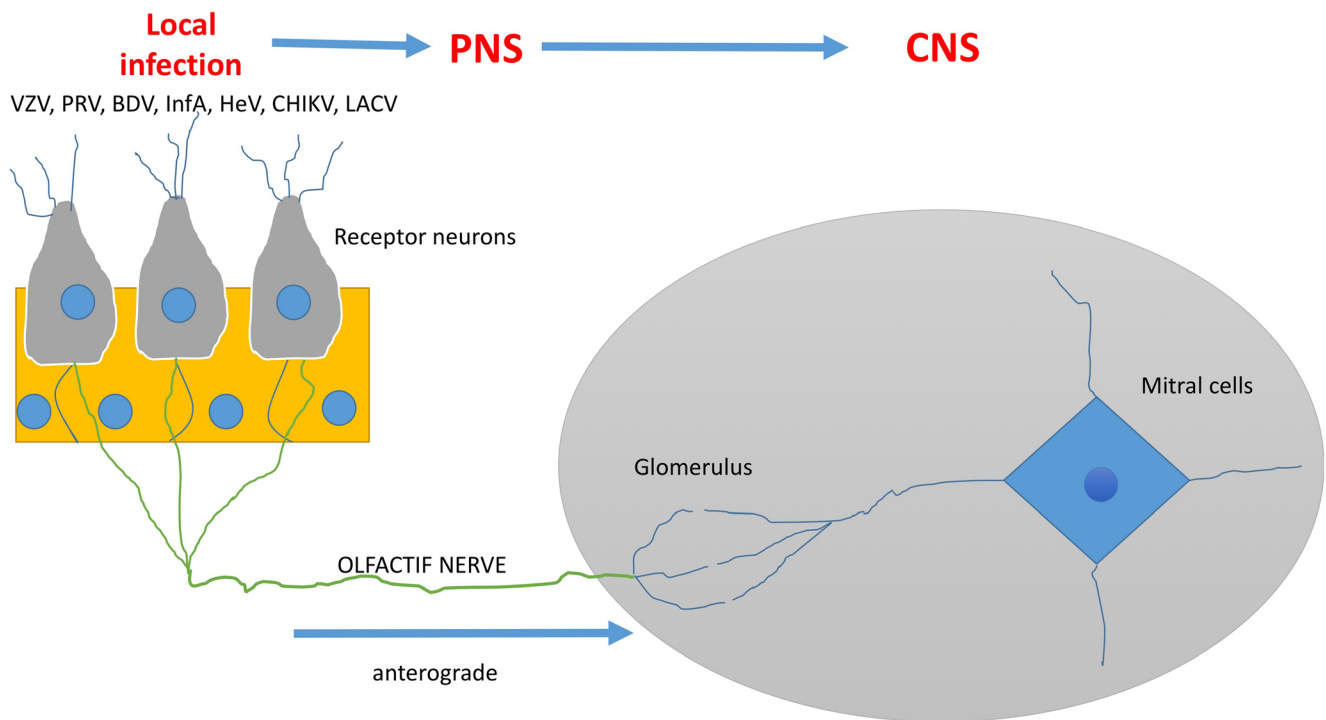


Fig. 2 Several viruses spread to the CNS by infecting the neuron receptor in the nasal olfactory epithelium to reach the brain by axonal transport along the olfactory nerve

[12]. These molecules also have a major function in the neuroplasticity and organization of neuronal networks and synapses. Such autonomous activation of neuronal cells using the innate receptors during viral infections could compromise neuroplasticity and the trigger subsequent neuronal dysfunction. Furthermore, viral infection-induced inflammatory

events show similarities to those observed in early neurodegenerative conditions, including altered expression of proteins relevant to axonal transport and synaptic transmission ([13]. [14]). In animal models of autoimmune encephalomyelitis (multiple sclerosis), the inflammation targets dendritic spines and leads to synaptic degeneration [15]. Additionally,

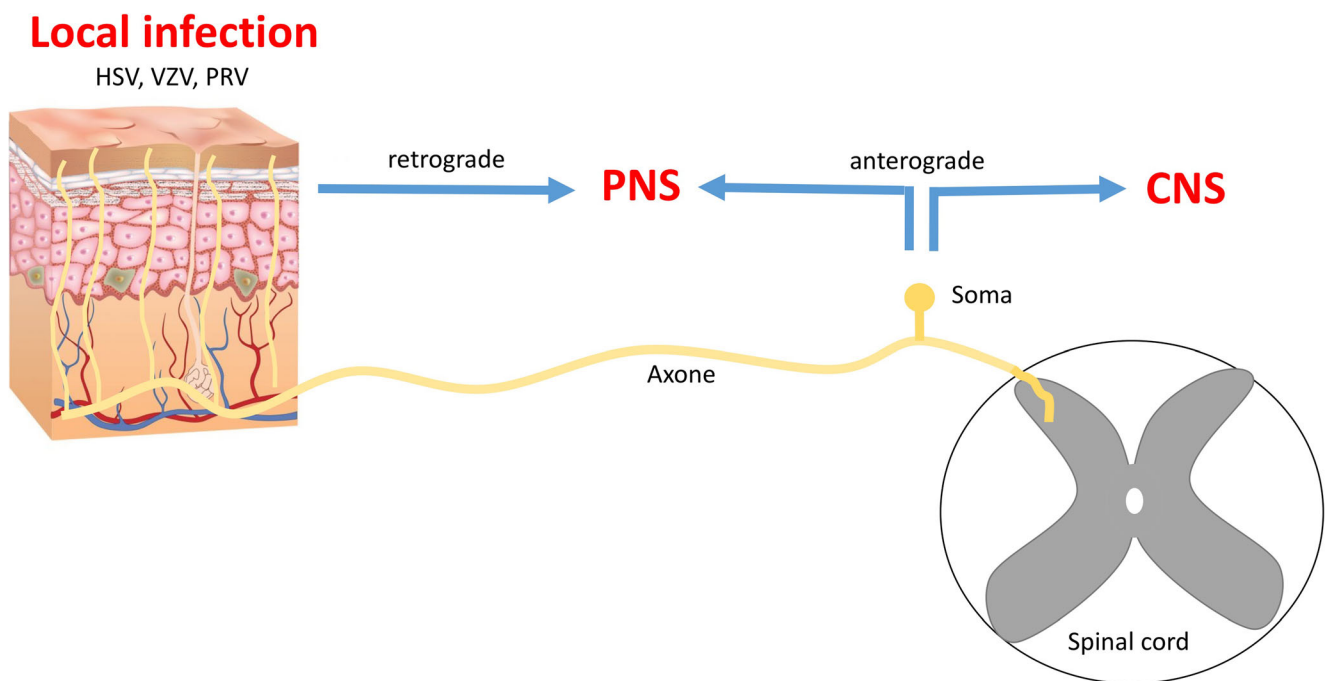


Fig. 3 Some respiratory viruses spread from the lungs to the CNS through the vagus nerve

synaptic dysfunction also occurs typically in the early stages of Alzheimer's disease pathogenesis [16].

Therefore, inflammatory reactions triggered by viral infections could initiate neurodegeneration, especially in individuals who are already at risk for neurodegenerative disorders as a result of the epigenetic differences that modulate the immune response or the individual's genetic makeup or susceptibility to infectious diseases [17].

The particularity of respiratory viruses in infected nervous system

Respiratory viruses such as respiratory syncytial virus (RSV) [18, 19], henipaviruses ([20, 21]), influenza A and B ([22]), and enterovirus D68 [23] are also sometimes found in the blood and, being neuroinvasive, they may use the hematogenous route to reach the CNS. These respiratory viruses can also use the olfactory nerve (Fig. 3) to reach the brain [1, 24, 25]. Furthermore, some of these viruses can use other peripheral nerves by targeting nociceptive neuronal cells in the nasal cavity and use the trigeminal nerve [26, 27], or in other cases, the sensory fibers of the vagus nerve in different organs of the respiratory tract [18, 28].

Several viruses spread to the CNS by infecting the neuron receptor in the nasal olfactory epithelium to reach the brain via axonal transport along the olfactory nerve.

Some viruses can spread by infecting the pseudounipolar sensory neurons of the PNS then anterograde axonal transport to CNS.

Influenza Virus (IV) is the most relevant viral etiology agent in respiratory tract infections. Several studies have shown that influenza A can be associated with neurological complications in both children and adults [29–31]. Several neurological pathologies related to influenza A infection have been described in the literature, including encephalitis [32], Guillain-Barre syndrome [33, 34], febrile seizure [35], acute necrotizing encephalopathy, and possibly acute disseminated encephalomyelitis (ADEM) [36]. In animal models, studies have shown that the routes of invasion used by IV are either the olfactory route in the nasal cavity or the sensory neurons of the vagus nerve in the lungs (Fig. 4). Thus, influenza A virus can affect cognition and behavior as long-term sequelae by altering the hippocampus and the regulation of neurotransmission [18, 37–40]. Other studies related to the influenza A virus show the risk of developing neurodegenerative diseases such as Parkinson's disease (PD) [41].

Coronavirus CoV is a group of non-segmented positive-sense RNA viruses belonging to the Coronaviridae family and the Nidovirales with four subfamilies: AlphaCoV (ACoV), BetaCoV (BCoV), DeltaCoV (DCoV), and GammaCoV [42]. CoV-OC-43 and CoV-229E are described as pathogenic in humans and are responsible for two beta coronaviruses (BCoVs) epidemics: the Middle East

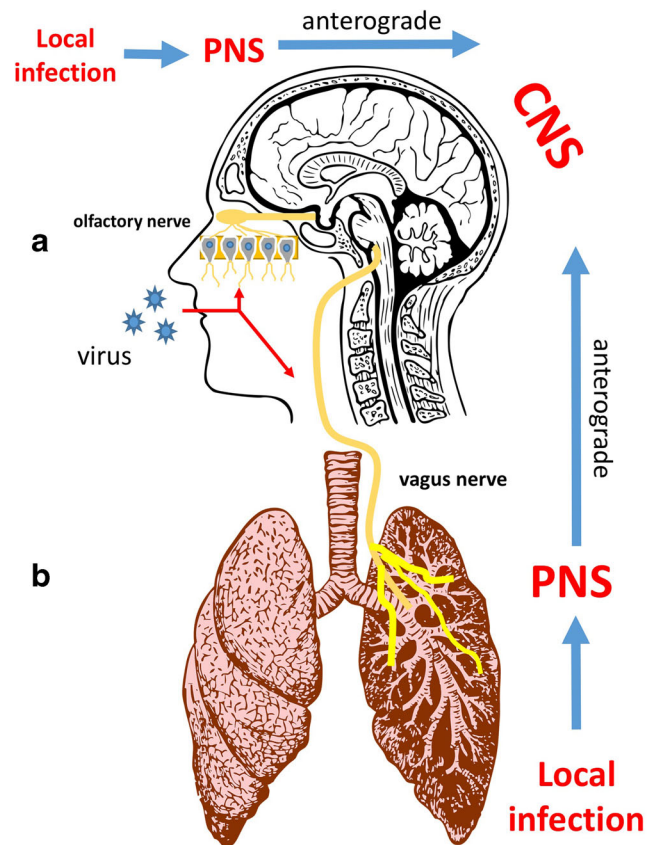


Fig. 4 **a** Several viruses spread to the CNS by infecting the neuron receptor in the nasal olfactory epithelium to reach the brain by axonal transport along the olfactory nerve. **b** Some respiratory viruses spread from the lungs to the CNS through the vagus nerve

respiratory syndrome (MERS-CoV) [43, 44], and Severe Acute Respiratory Syndrome (SARS-CoV) [45, 46].

The WHO declared that in December 2019, a series of viral pneumonia cases of unknown cause has erupted in Wuhan, Hubei, China (WHO Novel coronavirus report January 19, 2020) [47]. A sequencing analysis from respiratory tract samples showed a novel coronavirus, named 2019 novel coronavirus (COVID-19).

The last epidemics of SARS-CoV and MERS-CoV showed that CoV could cause extra-pulmonary pathologies most commonly in children as myocarditis, severe diarrhea, and multi-organ failure ([48–53]). Several studies described the neurotropic and neuroinvasive capabilities of CoV, through the hematogenous or neuronal retrograde route, leading to neurological pathologies such as multiple sclerosis and encephalomyelitis ([3, 54–56]); nevertheless, the capacity of CoV to infect the CNS is not well known ([57, 58]).

In 1980, Burks was the first to detect CoV in the CNS in an autopsy of patients with MS ([59]). In 2000, Arbour et al. reported a 67% case positive for CoV in a series of autopsy samples from patients with different neurological diseases, especially MS. In 2003, Hung et al. reported the first case of SARS-CoV infection with neurological manifestations [60]; a

59-year-old woman was first admitted with severe respiratory failure and seizures; in addition, the detection was also positive in both tracheal aspirates and CSF samples [60]. Lau et al. reported that viral genetic material was found in CSF samples of a 32-year-old woman with SARS-CoV infection [54]. SARS-CoV organ dissemination was reported in autopsy samples from patients that died of SARS-CoV. The autopsy showed the existence of viral RNA and SARS-CoV-N protein in the small intestine, liver, sweat glands, parathyroid, stomach, kidney, pituitary gland, and cerebrum, confirming the capacity of SARS-CoV to induce a systemic infection [61].

Furthermore, experimental studies show that transgenic mice infected intranasally with SARS-CoV-34 or MERS-CoV-13 had the virus detected in some specific brain areas (thalamus and brainstem) [62]. Some studies detected MERS-CoV virus only in the brain and not in the lungs with a high mortality rate [62]. Interestingly, the brainstem was the most heavily infected area of the brain either by SARS-CoV-34, 35 or MERS-CoV [62].

CoV are respiratory viruses with neurotropic capacities, which allow them to avoid the immune response and cause neurological complications associated with their infection. The mechanisms and routes to reach the CNS have not been well elucidated; the olfactory route and cranial nerves are the most plausible explanation for their invasion of CNS.

SARS-CoV-2 infected nervous system in COVID-19 patients

SARS-CoV and MERS-CoV cause lethal acute pneumonia with similar clinical signs and symptoms reported in pneumonia caused by SARS-CoV-2 in COVID-19 patients [60]. However, the literature suggests that the target of SARS-CoV-2 is the upper airway tract while SARS-CoV targets the lower airway tract, which is the main difference between these two viruses. The common symptoms of COVID-19 reported in a Wuhan local hospitals were fever, dry cough, and respiratory distress, most of which are the characteristic symptoms of COVID-19 ([60, 63, 76]).

As discussed above, the BCoV (SARS-CoV, MERS-CoV, CoV-229E, CoV-OC43) have neuroinvasive capabilities, and neurological manifestations have been documented ([62, 64, 65]). Although the routes of neuroinvasion is not well established, the invasion of peripheral nerve terminals, especially the olfactory and vagus nerve are most likely the reasonable routes that lead to CNS infection ([62, 65]).

Thus far, several studies provide direct evidence for the neurotropism of SARS-CoV-2 [66, 67]. Both SARS-CoV-2 and SARS-CoV bind to the ACE2 receptor to access human cells [68]. Because of the structural similarities and their target receptor, many SARS-CoV-mediated pathologies could also apply to SARS-CoV-2. A multiple number of studies have provided strong evidence for the neurovirulence and

neurotropism of SARS-CoV [69]. Several case report studies showed that CSF samples of a SARS patient who presented with tonic-clonic seizures tested positive for SARS-CoV, suggesting possible infection of the CNS by SARS-CoV [54]. Furthermore, Jun et al. isolated SARS-CoV from a specimen of brain tissue of a patient with SARS in which the pathological examination of the brain tissue indicated neuronal necrosis and glial cell hyperplasia [70]. In an autopsy study of eight cases with SARS, the viral particles and their genomic sequence were detected in the brain tissue of all cases. Six of them presented with edema and scattered red degeneration of the neurons [53]. Consistent with this, animal models suggest that the brain was the principal target organ for SARS-CoV in transgenic mice for human ACE2 receptor (*hACE2* mice) [71]. These findings of neurovirulence and neuroinvasion in SARS-CoV could provide strong circumstantial evidence of the neurotropic characteristics of SARS-CoV-2.

Similarity between SARS-CoV and SARS-CoV-2

The similarity in the pathologies between SARS-CoV and SARS-CoV-2 is becoming more and more evident. Recent studies showed a 79.5% genomic sequence homology between SARS-CoV and SARS-CoV-2 [131] and genetic similarities to bat coronavirus as high as 96% [72]. In a study based on the Homology and Phylogenetic Analysis of SARS-CoV and SARS-CoV-2 for a comparative purpose, the protein sequence using Blast showed that most of SARS-CoV-2 proteins are highly homologous (95–100%) to the proteins of SARS-CoV virus, in the comparative genomic analyses of SARS-CoV-2 and SARS-CoV using zpicture. The genomic sequences of SARS-CoV-2 and SARS-CoV have a high homology at the nucleotide level, with only six regions of difference (RD) in the genome sequence between SARS-CoV and SARS-CoV-2 [73]. The nucleocapsid protein in SARS-CoV-2 shares ~90% amino acid identity with that in SARS-CoV [74]. In addition, spike stalk S2 in SARS-CoV-2 are 99% identical to those of the two bat SARS-like CoVs (bat-SL-CoVZXC21 and bat-SL-CoVZC45) and human SARS-CoV [127].

The neuroinvasive capabilities in SARS-CoV are reported as a common feature of coronaviruses. This leads us to conclude that it is most likely that SARS-CoV-2 has a similar neuropathogenic potential, theoretically. The chronology of SARS-CoV-2 infection process includes manifestation of symptoms after 5 days of infection. Older patients and patients with immunodeficiency may develop respiratory failure in 8 to 15 days [76]. Consistent with this, SARS-CoV-2 has a long enough latency period for the invasion of peripheral nerve terminals which subsequently results in the invasion of the CNS.

Neurological manifestations of SARS-CoV-2 in patients with COVID-19

To date, there are only six reports describing the neurological manifestations of SARS-CoV-2 in patients with COVID-19 (Table 1), in which 173 of 756 patients had neurological manifestation. In a case report of 214 patients with COVID-19 in WHAN, China, neurological manifestation as acute cerebrovascular diseases and impaired consciousness were seen in 36.4% of all patients, and about 88% (78/88) of patients with serious complications ([125]). Moriguchi et al. reported a 24-year-old man admitted to hospital with transient generalized seizures with a Glasgow coma scale of 6 with hemodynamic stability. Before 9 days, the patient felt headaches, generalized fatigue, and fever. The RT-PCR test for SARS-CoV-2 was performed using a nasopharyngeal swab and CSF. Viral nucleic acids were detected in the CSF but not from nasopharyngeal swabs. This patient was diagnosed with meningoencephalitis due to SARS-CoV-2 infection [125].

In Beijing Ditan Hospital, Xiang et al. confirmed the presence of SARS-CoV-2 in the CSF of patients with COVID-19 clinically presented with viral encephalitis [78].

Similarly, Mingxiang et al. reported the same observation in a patient with SARS-CoV-2 presented with a viral meningoencephalitis in which SARS-CoV-2 was detected in the CSF.

SARS-CoV-2 can also damage the spinal cord and lead to acute myelitis [75]. Zahra et al. reports a case of a 65-years-old male admitted with acute progressive symmetric ascending quadriparesis that began with acute progressive weakness of

distal lower extremities. The patient had also facial paresis bilaterally 5 days before hospital admission. Two weeks later, the patient suffered from cough, fever, and sometimes dyspnea. RT-PCR for COVID-19 was positive. In this study, Guillain-Barre syndrome in a patient infected with COVID-19 was reported (2020) [128].

Hua et al. reported a case of a 61-years-old woman admitted with progressive weakness in both legs and severe fatigue. Four days before she returned from Wuhan, without fever, cough, chest pain, or diarrhea. The patient was diagnosed with Guillain-Barre syndrome associated with SARS-CoV-2 infection [129].

The olfactory epithelium and olfactory dysfunction in COVID 19 patients

SARS-CoV-2 is characterized by the high infectivity due to glycoprotein spike considered as the important factor accelerating the spread of COVID-19. The spike leads the virus to bind to the host receptor with much higher affinity as compared to related SARS-CoV virus. Recent reports indicate that the early marker of SARS-CoV-2 infection is anosmia or partial loss of the sense of smell (hyposmic). In a study of 357 patients, 85.6% had olfactory dysfunction related to the SARS-CoV-2 infection, 284 (79.6%) patients were anosmic, and 73 (20.4%) were hyposmic [79]. This manifestation may be considered as direct damage to the olfactory receptor neurons located in the olfactory epithelium. Additionally, cells located in the olfactory epithelium (neuronal and nonneuronal cells) express both ACE2 and TMPRSS2 protein receptors required for efficient SARS-CoV-2 infection in humans ([80]. [81]). Some studies showed that TMPRSS2 protein

Table 1 Literature review of 765 COVID-19 patients, in which 18% had neurological symptoms and complications, including encephalopathy, encephalitis and cerebrovascular pathologies, acute myelitis, and Guillain-Barré syndrome

Author and year	Series type	Patients (n)	Patients with Neurological manifestations (%)	Type of neurological manifestations (%)
Mao et al.; [75]	Retrospective case serie	214	36	Headache (13%); dizziness (17%); impaired consciousness (8%); acute cerebrovascular problems (3%); ataxia (0.5); seizures (0.5%)
Wang et al. [76]	Retrospective case serie	138	16	Dizziness in 9%; headache in 7%
Chen et al. [63]	Retrospective case serie	99	17	Confusion in 9%; Headache in 8%
Huang et al.; 2020 [133]	Retrospective case serie	41	8	Headache in 8%
Yang et al.; [77]	Retrospective case serie	52	6	Headache in 6%
[134]	Retrospective case serie	221	6	5% developed acute ischemic stroke; 0.5% had cerebral venous sinus thrombosis; 0.5% had cerebral hemorrhage
Total		765	18	Headache in 42%

receptors is expressed on neuronal cells and likely facilitate SARS-CoV-2 brain infection through the anterograde axonal transport along the olfactory nerve (Fig. 2) [81, 82]. SARS-CoV-2 can reach the brain if the virus first invades high ACE2 expressing, yet unidentified nonneuronal, cells in the olfactory epithelium and then pass to low ACE2 expressing mature neuronal cells to be transported along olfactory axons to the brain.

In animal models, some studies showed that the expression of murine ACE2 and TMPRSS2 have the tendency to increase with age as determined by microarray analysis [82]. If this is the case for humans, then in elderly people, the olfactory epithelium may be more sensitive to SARS-CoV-2 accumulation.

To understand the antiviral protective immune responses of neuronal cells in the olfactory epithelium, a recent study in fish shows that neuronal cells initiate ultrarapid immune responses in the olfactory epithelium after binding rhabdovirus surface glycoprotein [83]. Additionally, the activation of the pro-inflammatory effects inhibits the uptake of the virus into ciliated dendrites/soma and subsequent anterograde axonal transport along the olfactory nerve to reach the brain. As a result, infected neurons undergo apoptosis, which may eliminate initiation of olfactory stimuli and anosmia.

Based on the above observation, infected people with SARS-CoV-2 who show signs of olfactory dysfunctions may actually represent those individuals with faster and stronger initiate immune response against the SARS-CoV-2 infection. Noteworthy that older patients who are much more sensitive to SARS-CoV-2 infection also have degenerative dysfunctions in their neuronal cells in the olfactory epithelium. This is consistent with the observation that elderly patients have more severe COVID-19 symptoms most likely due to the attenuated early immune response.

The anatomical perspective in COVID-19 infection

In experimental studies using transgenic mice, SARS-CoV-34, 35 or MERS-CoV was found in the brain and very heavily in the brainstem [62]. It is known that some respiratory viruses can reach the brain by the retrograde route via infecting the sensory fibers of the vagus nerve in different organs of the respiratory tract [18, 28]. The vagal nucleus consists of four nuclei, including the ambiguous nucleus located in the medulla oblongata in the brainstem [84]. Additionally, the basic respiratory rhythm is generated in the central respiratory neuron network located in various sites in the lower brainstem, more specifically, ventral to the ambiguous nucleus and the dorsal motor nucleus of the vagus, and the area postrema, which are then output as motor activities generated to regulate the respiratory rhythm [85]. Therefore, it is plausible to hypothesize that if SARS-CoV-2 reach the brain through the vagus nerve, the virus will invade the brainstem starting with

the vagal nucleus and surrounding sites including the respiratory control center which can lead to more respiratory dysfunction that further exacerbate the damage caused by the primary infection in the lungs.

Neuropathologies and sequelae related to SARS-CoV-2 infections

Some studies describe the persistence of CoV RNA in the human CNS [86]. In experimental studies, mice who survived acute encephalitis caused by CoV showed a long-term sequelae, including the hypo-activity in an open field test, decreased hippocampus excitability with concomitant neuronal loss in the CA1 and CA3 [87]. Similar results in studies with infection by the influenza A virus and RSV [88–90] infection by West Nile virus (WNV) showed the same neuronal loss in the CA3 [91].

A patient with COVID-19 was diagnosed with necrotizing hemorrhagic encephalitis after presenting with altered mental status. CT images showed a symmetric hypo-attenuation in medial thalami bilaterally and MRI confirmed a hemorrhagic lesions in the bilateral thalami, subinsular regions and medial temporal lobes [92]. In a case report of a 24-year-old man, he presented headaches, generalized fatigue, fever, with generalized seizures, and altered mental status that progressed and led to impaired consciousness. Clinical and laboratory diagnosis was viral meningoencephalitis and RT-PCR analysis of the CSF confirm the SARS-CoV-2 infection. Brain MRI showed changes in the right mesial temporal lobe, the right wall of the lateral ventricle, and the hippocampus. Interestingly, the nasopharyngeal swab specimen for RT-PCR was found to be negative for SARS-CoV-2, which means that COVID-19 may have independent mechanisms of neuropathogenesis [125].

Xu et al. reported in an autopsy study that edema has been detected in the brain tissue of COVID-19 patients due to the hypoxia caused by SARS-CoV-2 [73]. This means COVID-19 patients have the potential to develop infectious toxic encephalopathy due to the hypoxia and viremia. The essential pathological changes in this disease are cerebral edema, with no evidence of inflammation from CSF analysis [130].

A significant amount of evidence shows that respiratory infection is an independent risk factor for acute cerebrovascular disease [94, 95]. Experimental mouse models suggest that some respiratory viruses as influenza can aggravate ischemic brain injury and increase the risk of cerebral hemorrhage by triggering a cytokine storm [96]. As previously discussed, SARS-CoV-2 causes cytokine storm syndromes, which may be one of the factors that patients with COVID-19 can develop acute cerebrovascular disease [63, 97]. Furthermore, SARS-CoV-2 infections often show elevated levels of D-dimer and severe platelet reduction in patients with critical conditions,

which may increase the chance of acute cerebrovascular events [76].

Cerebrovascular diseases and SARS-CoV-2 infections

A meta-analysis of 46,248 infected patients in 8 studies from China showed that the most prevalent comorbidities were hypertension (17%) and diabetes mellitus (8%), then cardiovascular diseases (5%) [77, 98]. This indicates that COVID-19 and stroke share similar risk factors. There is strong evidence that the severity of COVID-19 infection is directly linked to the presence of cardiovascular comorbidities [99]. In a case series from Wuhan of 214 patients with COVID-19, 14 patients developed strokes. The study concluded that patients with cardiovascular risk factors were more likely to develop acute cerebrovascular diseases [75]. Similarly, 4 COVID-19 patients with cardiovascular risk developed stroke. The mechanism of vascular damage in all these patients was the large vessel disease [100]. An observational study showed that in 221 COVID-19 patients, 5% developed acute ischemic stroke, 0.5% cerebral hemorrhage, and 0.5% cerebral venous sinus. The incidence was higher in older patients with cardiovascular risk factors [101].

COVID-19 and multiple sclerosis

The etiology of several long-term neuropathologies is still not well known, such as multiple sclerosis (MS), in which a viral infection may play a role in the pathogenesis in genetically predisposed individuals [102–106]. Over the last decades, several viruses have been associated with MS, based on detection of viral nucleic acids, virions, or viral proteins in the CNS or the presence of antiviral antibodies in the serum and/or cerebrospinal fluid. In 1980, for the first time, the association of coronaviruses with MS was suggested for by their isolation from the CNS of two patients [59].

Since then, multiple studies have linked human coronaviruses (including CoV-OC-43 and CoV-229E) with MS. In several autopsy studies, the coronavirus-like particles were detected in brain material obtained from MS patients [107] and in other studies, viruses molecularly related to murine neurotropic coronaviruses were detected in the brain tissue from MS patients [59]. Additionally, anti-HCoV intrathecal antibody synthesis, indicative of a CNS infection, was reported in MS patients [108]. Furthermore, HCoV RNA was detected in the brain [109–111] and in the cerebrospinal fluid of MS and other neurological disease (OND) patients [112]. Coronavirus antigens were also detected in MS patient brains [109, 110].

Interestingly, in an autopsy studies of 90 patients with MS, viral RNA was present in a large number of samples; 48% (44 of 90) of all donors were positive for one or both

viral strains (CoV-OC-43 and CoV-229E). HCoV-OC43 RNA was widely detected in normal white and gray matter as well as in plaques of MS patient brains. This study also suggested that HCoV-OC43 has the capacity to persistently infect cells in the human CNS and that such infections could lead in some cases to specific molecular adaptation of this virus to the CNS environment [57]. Consistent with this, in animal model studies, a persistent coronavirus infection provoked a chronic demyelination in genetically predisposed mice through immune reaction-mediated mechanisms [113].

There are multiple possible mechanisms by which a viral infection could induce a demyelinating disease such as MS-like lesions. It could be induced as a direct consequence of viral infection such as lytic infection of oligodendrocytes [114]. Alternatively, it could be indirectly mediated through the expression of cytotoxic molecules by glial cells such as MHV-induced chronic demyelination in the CNS. In the latter, several inflammatory molecules, such as IL-6, tumor necrosis factor, interleukin 1 β (IL-1 β), type 2 nitric oxide synthase [115], RANTES, cytokine response gene 2, and macrophage-inflammatory protein 1 β , or their mRNAs, were detected [116].

The HCoV-OC43 virus was detected in the CNS of a child with acute disseminated encephalomyelitis (ADEM) [55] which is another demyelinating neurological disorder characterized by neuroinflammation after nonspecific upper respiratory tract infections. Even though the etiological agent remains unknown, several studies suggest that human coronaviruses can lead to ADEM. Subacute panencephalitis sclerosis (SSPE), a progressive fatal neurological disease, is also clearly linked to a viral infection as the persistence of measles virus within the CNS [117].

Viral infection of oligodendrocytes could lead to demyelinating disease through the alteration of their normal function or cytolysis as is the case for reactivated human polyomavirus, which induces the progressive lysis of oligodendrocytes during progressive multifocal leukoencephalopathy [118, 119]. The release of myelin components could also trigger an autoimmune attack. Infection or activation of astrocytes and microglia could lead to release of inflammatory mediators that could damage oligodendrocytes, therefore exacerbating the pathology [120–123].

It has been shown that CoV-OC-43 is responsible for encephalitis with a T cell response to the infection [124]. This underlines the possibility that the trigger for long-term demyelinating neuropathologies such as MS-like lesions in patients with respiratory viruses is the immune response. Considering the phylogenetic studies and the similarities between SARS-CoV-2 and all beta coronaviruses, including the lineage A groups prototypical coronaviruses, we can conclude that even if the genotype of the virus itself can play a role in the

pathogenesis of MS-like lesions associated to viral infection and CoV-OC-43 and CoV-229E may be considered as a risk factor to develop MS. Taking into account the similarities between SARS-CoV-2 and CoV-OC-43 and CoV-229E as well as the characteristics of the immune response to SARS-CoV-2 infection including to the cytokine storm and the surge of IL-6, tumor necrosis factor, interleukin 1 β (IL-1 β), and type 2 nitric oxide synthase, it is almost certainly that SARS-CoV-2 may be responsible for MS-like demyelinating lesions as a long-term consequences of COVID-19.

Conclusion

Based on the available data, it is highly likely that respiratory distress is not only the result of pulmonary inflammatory structural damage, but also due to the damage caused by the virus in the respiratory centers of the brain, making it more difficult to manage these patients.

Several human respiratory viruses can have neuroinvasive and neurotropic capabilities, leading to neuropathological consequences in vulnerable populations. Understanding the consequences of neuroinvasion and the underlining mechanisms of respiratory viruses (including coronaviruses) and their interactions with the central nervous system is essential as it can be used to better understand the potential pathological relevance of the infection, in addition to the design of novel diagnosis and intervention strategies that will help uncover the potential druggability of molecular virus-host interfaces highly relevant to symptoms of various neurological diseases with a viral involvement.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was waived by the local Ethics Committee of Cadi Ayyad University, Faculty of Medicine and Pharmacy Marrakech in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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