Review

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Does coronaviruses induce neurodegenerative diseases? A systematic review on the neurotropism and neuroinvasion of SARS-CoV-2

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SUMMARY The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in 2019 in Wuhan, China. Clinically, respiratory tract symptoms as well as other organs disorders are observed in patients positively diagnosed coronavirus disease 2019 (COVID-19). In addition, neurological symptoms, mainly anosmia, ageusia and headache were observed in many patients. Once in the central nervous system (CNS), the SARS-CoV-2 can reside either in a quiescent latent state, or eventually in actively state leading to severe acute encephalitis, characterized by neuroinflammation and prolonged neuroimmune activation. SRAS-CoV-2 requires angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor. The expression of this receptor in endothelial cells of blood-brain barrier (BBB) shows that SRAS-CoV-2 may have higher neuroinvasive potential compared to known coronaviruses. This review summarizes available information regarding the impact of SRAS-CoV-2 in the brain and tended to identify its potential pathways of neuroinvasion. We offer also an understanding of the long-term impact of latently form of SARS-CoV-2 on the development of neurodegenerative disorders. As a conclusion, the persistent infection of SRAS-CoV-2 in the brain could be involved on human neurodegenerative diseases that evolve a gradual process, perhapes, over several decades.

Keywords SRAS-CoV-2, neurotropism, neuroinvasion, neurodegenerative diseases

1. Introduction

Coronaviruses (CoVs) are positive-sense RNA viruses that belong to the Coronvirinae subfamily, in the Coronaviridae family of the Nidovirales order (*1*). This family is classified into four subgroups alpha, beta, gamma, and delta. Alpha- and beta-coronaviruses infect only mammals, usually causing respiratory symptoms in humans and gastroenteritis in animals (*2*). All CoVs caused diseases to humans have had animal origins such as bats (*3*). Currently, there are seven CoVs that can infect humans: HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV-1 and SARS-CoV-2 (*4*). Four of these CoVs: HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1 have usually caused influenza symptoms and the last three CoVs have caused pandemics in the past two decades (*5,6*), while HCoV-229E and HCoV-OC43, besides SARS-CoV-1 have been shown to infect neurons (*6*).

SARS-CoV-2, which shares highly homological sequence with SARS-CoV-1, is responsible for the current COVID-19 outbreak with more than 70 million patients diagnosed and over 1,612,000 deaths. These statistics exceed the total of SARS-CoV-1 and MERS-CoV in 2002 and 2012, respectively (*5*).

CoVs are named for the crown-like spikes on their surface. To gain access to host cells, CoVs rely on spike proteins (S), which are membrane-anchored trimers containing a receptor-binding S1 segment and a membrane-fusion S2 segment (*7*). The S1 contains a receptor-binding domain (RBD) that binds to a host cell receptor. SARS-CoV-2 are also covered by spike proteins that contain a variable RBD. RBD binds to angiotensin-converting enzyme-2 (ACE2) receptor expressed in all tissues with greatest activity in the ileum and kidney followed by heart, brain, lung, vasculature, stomach and liver (*7,8*).

The binding of the S to the ACE2 receptor is correlated with viral infectivity in the targeted tissue and governs clinical outcomes (*9*). For example, binding of the SARS-CoV-2 to the ACE2 receptor in the type II pneumocytes in the lungs, triggers a cascade of inflammation in the lower respiratory tract (*5*). In fact, 98% of COVID-19 patients developed clinical pneumonia with hypoxic respiratory failure in the first wave of the pandemic (*1,5*). Consequently,

clinicians concluded that this infection alters not only the respiratory function but also the cardiovascular homeostasis (*10*).

Despite the short duration of the current pandemic outbreak, several neurological and neuroradiological phenotypes have been reported including headache, anosmia and ageusia (*11,12*), followed by muscle soreness, then altered consciousness. Given the lack of data regarding the neurotropism of SRAS-CoV-2, we will try to gain more insight into its characteristics based on those of other CoVs. Indeed, in light of the structural similarity between SARS-CoV-2 and others betacoronaviruses, it is highly suspected that all CoVs have similar neuroinvasive and neurotropic properties. Indeed, SARS-CoV-1 and SARS-CoV-2 have comparable binding affinities achieved by balancing energetics and dynamics (*13,14*).

Though the understanding of the pathogenetic mechanisms underlying the neuroinvasion will be revealed in time, there is an urgent need to answer the questions of whether SARS-CoV-2 is neurotropic and whether it contributes to post infectious neurodegenerative diseases.

2. Neurological manifestations

Information about neurological manifestations in COVID-19 patients is still scanty. However, it is now well-known that SRAS-CoV-2 may invade the brain inducing neurological diseases. Such neuroinvasive property of CoVs has been well documented almost for SARS-CoV-1, MERS-CoV, HCoV-229E, HCoV-OC43, mouse hepatitis virus (MHV), and porcine hemagglutinating encephalomyelitis coronavirus (HEV) (*15*).

The first study about neurological disease following SRAS-CoV-2 virus infection was reported during March 2020. Indeed, researchers from Beijing Ditan Hospital, China, described and confirmed patient with COVID-19, whose cerebrospinal fluid (CSF) was tested positive for SRAS-CoV-2, by gene sequencing (*16*). Another study evaluated 214 patients diagnosed with COVID-19 from China of which 36% had neurological manifestations, including acute cerebrovascular disease and impaired consciousness (*17*). A recent study from France reported neurologic issues in 58 of 64 patients with COVID-19, including encephalopathy, prominent agitation and confusion (*18*). The most common neurologic symptoms in COVID-19 clinical cases are headache, anosmia, and ageusia. Interestingly, these three neurological manifestations occurred in early stage of the disease and therefore could be considered as a predictor of clinical impairment. Besides, other neurological findings include stroke, impairment of consciousness, and encephalopathy are showed. All these informations advocate a possible neuroinvasion and neurotropism of SARS-CoV-2.

3. Neuroinvasion of SARS-CoV-2

The following section tempt to elucidate two features: (*i*) how certain patients develop neurological disease after SARS-CoV-2 infection? and (*ii*) whether the virus acts directly or indirectly towards neurons?

As for the route of SARS-CoV-2 entering the CNS, the hematogenous one's appears to be likely the pathway for virus to reach the brain, although the existence of BBB. In addition, neuronal pathway is also reported to be an important vehicle for neurotropic viruses to enter the brain. SARS-CoV-2 can across the cribriform plate of the ethmoid bone in proximity to the olfactory bulb (*11,19,20*). In fact, SARS-CoV-2 may first invade peripheral nerve terminals, and then gain access to the CNS *via* a synapse-connected route in a way of retrograde or anterograde transport. Also, leukocyte migration across the BBB could be a plausible route of viral neuroinvasion (*21*). In the following part, we will documented the putative routes for SARS-CoV-2 neuroinvasion that are summarized in Figure 1.

3.1. Infection *via* blood-brain barrier spread

The blood-brain barrier is a highly selective barrier critical for CNS homeostasis. BBB controls peripheral blood-brain exchange and prevents toxins and pathogens from access to the CNS. The functional and structural integrity of the BBB mainly relies on specific features of the brain microvascular endothelial cells (BMECs) lining the brain capillaries. These cells are tightly connected by an assembly of adherens and tight-junction complexes (*22*). Despite the complex structure of BBB, consisting in astrocytes, pericytes and endothelial cells, neuroviruses have evolved to disrupt and evade it (*23*). Two possible mechanisms for SARS-CoV-2 spread across the BBB are hypothesized: (*i*) the first one is through infection of BMECs and (*ii*) the second mechanism by leukocytes infection that pass through the BBB. Therefore, the possible hallmark of SRAS-CoV-2 neuropathogenesis is the disruption of the BBB.

SRAS-CoV-2 viruses may compromise also the integrity of BBB by either infecting or inducing cellular damage to the neurovascular unit or by eliciting innate and adaptive immune responses leading to neuroinflammation (*24*). BBB invasion by SRAS-CoV-2 correlates with virus-induced disruption of tight junctions on BMECs, leading to BBB dysfunction and enhanced permeability. Indeed, BMECs have already been reported as potential cell targets for CoVs viruses such as MHV (*25*) since they express ACE2 receptor (*26*). S protein of SRAS-CoV-2 can interact with ACE2 on the BMEC cell surface and can infect endothelial cells, facilitating the entry of virus into the CNS, may be without disturbing the BBB. Although BBB disruption can be observed later, accompanied by the degradation of tight junctions proteins and an increase in MMPs (*25*). This hypothesis

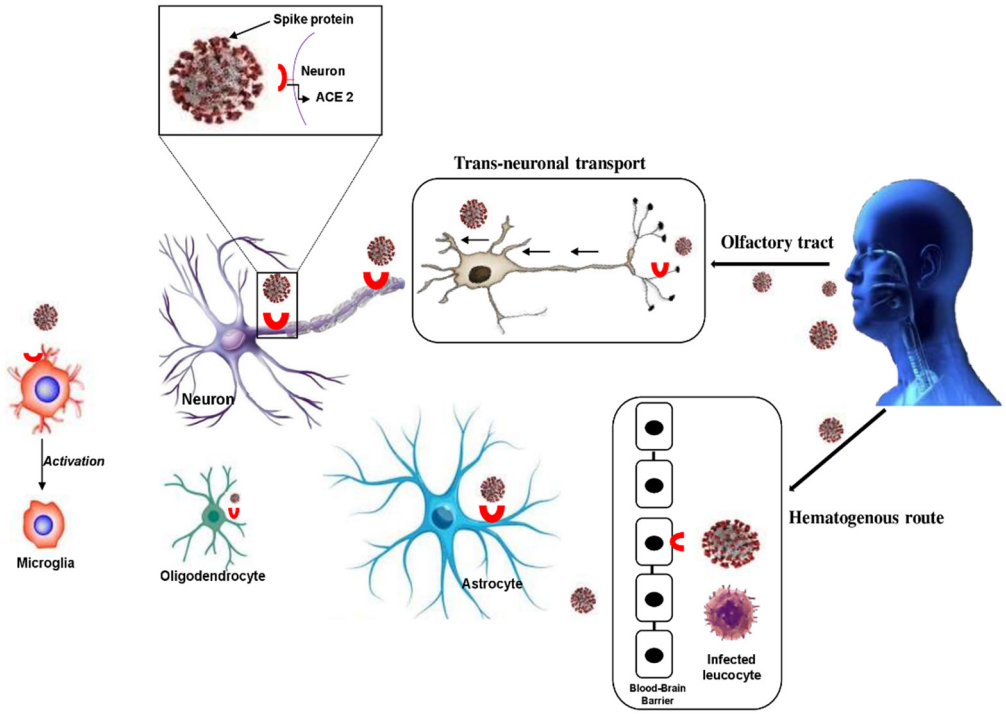

Figure 1. Putative routes for SARS-CoV-2 neuroinvasion. The most specific routes where SARS-CoV-2 enters the brain are: (*i*) Hematogenous route *via* blood-brain barrier (BBB), SARS-CoV-2 induces direct infection of the neurovascular unit in the BBB. So, infected migrating leukocyte cross BBB freed to infect local neuronal cells. (*ii*) Trans-neuronal route: SARS-CoV-2 could enter the nervous system through peripheral nerve fibers including the olfactory receptors, the pulmonary network and the enteric nervous system. ACE2: angiotensin-converting enzyme 2.

can be confirmed by data regarding viral replication of SRAS-CoV-2 in BMECs. In the other hand, reduced expression of tight junctions proteins is a characteristic feature of BBB disruption by neurotropic viruses such as Japanese encephalitis virus (JEV) (*27*), West Nile virus (WNV) (*28*), and human immunodeficiency virus type 1 (HIV-1) (*29*). In fact, these viruses induced a downregulating transcription level of tight junctions mRNA (*30*).

Disruption of tight-junction complexes is often associated with enhanced generation of reactive oxygen species (ROS). Viral infection in target cells can induce mitochondrial damage or NADPH oxidase activation, resulting in high ROS generation (*31*) engendering detrimental effects (*32*). Indeed, ROS can target all biological molecules, including lipid, protein, and nucleic acid, resulting in the release of various cytokines and proteases that damage vasculature in BBB (*31*). In addition, astrocytes are also prone to oxidative stress (*33*). This is confirmed by Masanetz and Lehmann showing that, exposure to viral proteins such as HIV-1 increase astrocyte sensitivity to redox insults (*34*).

In the other hand, SARS-CoV-1 has been shown to infect lymphocytes, granulocytes and monocytes, which all express ACE2 (*35,36*). Infected leukocytes thwart the BBB *via* diapedesis like the "Trojan horse"mechanism (*37,38*). However, it has been demonstrated that T lymphocytes allow SARS-CoV-2 infection but do not support viral replication (*19,26*).

Accordingly, the systemic inflammation, that characterizes COVID-19, increases the permeability of the BBB, thereby allowing infected immune cells, cytokines, and possibly virus might pass into the CNS and interact with ACE2 on neurons and glia (*39*). Thus, BBB plays a key role in the pathogenesis of neurotropic viruses by controlling the access of immune cells or viruses into the CNS. Once the virus gains access to neuronal tissue, it could begin a cycle of viral budding and further damage neuronal tissue.

3.2. Infection *via* viral trans-neuronal spread

According to clinical studies, CoVs neuroinvasion could plausibly be achieved by (*i*) transsynaptic transfer across infected neurons and (*ii*) entry *via* the olfactory nerve.

The olfactory system, a well-known route of entry for human viruses into the CNS, is connected to the limbic structures of the brain, providing a possible path for viruses to infect the CNS. In the litterature, a number of neurotropic viruses including Theiler's murine encephalomyelitis virus, and WNV are known to rapidly disseminate throughout the CNS by olfactory transmission in animal models (*28,40*).

In the few recent report, the nasal cavity is the main gate for SARS-CoV-2 entrance (*19,21*). Notably, the olfactory epithelium (OE) is a suitable source of biological samples for early SARS-CoV-2 detection. OE is a continuously regenerating tissue containing both

neuronal and non-neuronal cells. Therefore, olfactory tract becomes an important channel for SARS-CoV-2 transmission to the brain.

In the other hand, CoV has been shown to spread retrograde *via* transsynaptic transfer using an endocytosis or exocytosis mechanism and a fast axonal transport mechanism of vesicle transport to vehicle virus to neuronal cell bodies (*19*). For instance, HIV and HCoV-OC43 have all been shown to use retrograde fast axonal transport to infect the neurons (*41*). Herein, neuronal expression of ACE2 facilitate SARS-CoV-2 infection through the uptake into dendrites and soma (*21*). Once in CSF, the virus could reach most of the brain areas including the brainstem where cardiorespiratory controlling nuclei are located (*42,43*). Moreover, there is an ACE2 activity in the rostral ventrolateral medulla region in the brainstem. As previously shown, SRAS-CoV-1 and MERS-CoV can invade brainstem *via* a synapse-connected route from the lungs (*21,44,45*). Thus, neuroinvasion of SARS-CoV-2 in the brainstem may be one reason for the acute respiratory failure (*46,47*).

4. Neurotropism of SARS-CoV-2 and inflammation

It is not yet confirmed whether SARS-CoV-2 induced inflammation in the animal or human brain; however, it is well established in the literature that other CoVs target the brain and cause inflammation and encephalomyelitis. For example, human HCoV-OC43 has been associated with encephalitis in children (*48*). In addition, SARS-CoV-1 RNA has been detected in the CSF of a patient with SARS (*49*). Further studies showed that human HCoV-OC43 as well as animal CoVs reach the CNS and cause encephalitis (*50*). However, there remains the question of how the tropism of SRAS-CoV-2 can mediate the acute inflammation in the brain. We can response to this question based on the scientific data reporting that once in the brain, SRAS-CoV-2 replicates on endothelial cells on the BBB receptor and on neuron before targeting astrocytes, oligodendrocytes, and microglia. In addition, it is recently showed that ACE2 is expressed in neurons, astrocytes, and oligodendrocytes (*19*) (Figure 2). Interestingly, ACE2 was shown to be highly concentrated in the substantia nigra, ventricles, middle temporal gyrus, and posterior cingulate cortex (*39*).

When SRAS-CoV-2 reach the brain, the innate immune system serves as the first line of host defense against infection. It detects viral infection through the recognition of pathogen-associated molecular patterns by pathogen-recognition receptors (PRRs) including Toll-Like Receptors (TLRs). Following infection, neurovirulent CoVs manifests significant upregulation of inflammatory cytokines, chemokines, and MMPs, all of which serve to initiate a cell anti-viral response (*51-53*). Other cells including neutrophils and macrophages are the primary innate immune cells recruited into the CNS immediately following CoVs infection (*54,55*). Herein, SRAS-CoV-2 induced TNF-α, IL-6, CCL2, and CXCL10 production; possibly with the inhibition of protective IFN-β production by BMECs (*56*).

In the other hand, TLRs contributes in providing the host against CoVs infection (*57*). Indeed, it has been demonstrated that TLR3 and TLR7 signaling restricted neurotropic infection of WNV in neurons (*58,59*). Thus, TLR3 and TLR7 enhanced BBB permeability after viral neuroinvasion. Equally important is the recent

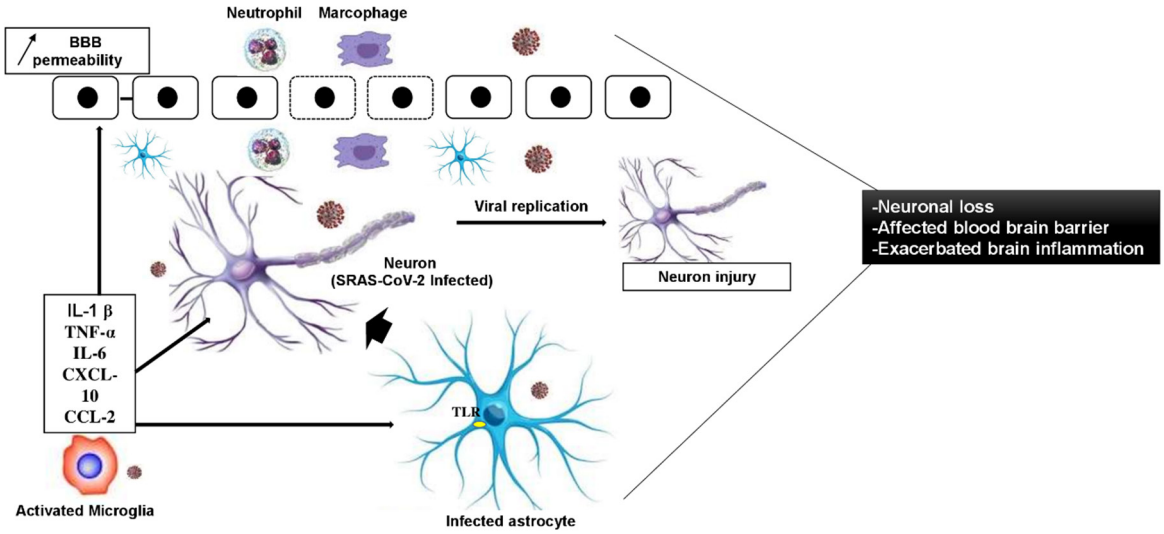

Figure 2. Schematic representation of the acute inflammation during SRAS-CoV-2 infection. Once neurons are infected, the virus begins multiplying and replicating, which causes the first round of neuronal injury accompanied by the production of cytokines or chemokines. These cytokines/chemokines activate microglia and astrocytes, which in turn stimulates more production of proinflammatory cytokines/chemokines and contributes to further neuronal injury. Also, cytokines and chemokines can activate immune cells inside the brain that initiate and/or potentiate BBB dysfunction and alter the architecture of tight junctions on BBB. Furthermore, transendothelial migration of leukocytes (macrophage and neutrophil) causes acute neuronal tissue damage. BBB: blood brain barrier; TLR: Toll-Like Receptors.

demonstration that the activation of TLR-2 and TLR-4 was reported during MHV infection of astrocytes, with subsequent IFN type-I expression and up-regulation of IL-6 cytokine, which was dependent of viral replication (*60*). Indeed, MHV-A59 and SARS-CoV-2 have multiple similarities such as a proinflammatory cytokine reaction involving IL-6 (*60,61*).

On another side, if the innate immune system fails to confine SRAS-CoV-2, the adaptive one will be activated as it is slow, systemic, and virus-specific, leading to stimulation of the immunological memory. The adaptive immune response includes usually cell-mediated immunity and humoral immunity and involves the action of $CD4^+$ T helper cells, $CD8^+$ cytotoxic T cells and B cells. Herein, SRAS-CoV-2 infection might be removed by the action of T cells of the adaptive immune response and virus-specific antibodies. Nevertheless, viral infections may spread to all CNS tissues if the virus escapes from the immune system, causing increased virus replication or overreactive innate immune responses. Subsequently, activation of glial cells by SRAS-CoV-2 viruses results in the production of multiple inflammatory chemokines and cytokines. In fact, CoV strains such as MHV were shown to activate astrocyte that can be a source of CCL5 and CXCL10 (*62,63*).

Noteworthy, activated microglial cells can be the major source of TNF-α, which can be deleterious to neurons (*64*). Thus, the elevated levels of the proinflammatory cytokines IL-6, IL-15, IL-1β and TNF-α in the CNS could induce irreversible neuronal damage (*64*). Additionally, previous studies showed that when CoVs attacked glial cells, a large amount of inflammatory factors such as IL-12, IL-16, IL-17, and IL-18 were released (*60*). Also, the elevated levels of the chemokine CCL2 in the infected CNS by SRAS-CoV-2 could establish an inflammatory and immunosuppressive environment (*65*). Therefore, inflammatory factors can be one of the pathophysiological processes of brain damage.

As shown in Figure 3A, the storm of cytokines that is up-regulated following SRAS-CoV-2 infection consists of proinflammatory cytokines, which would normally be associated with the recruitment of inflammatory cells, including lymphocytes and macrophages, to the site of infection.

In summary, infected neurons by SRAS-CoV-2 viruses may produce chemokines that can also induce the activation of glial cells, which in turn produce a preponderance of inflammatory chemokines and cytokines (Figure 3A). These inflammatory mediators can break down the BBB by reducing the integrity of the tight junctions between BMECs. Inflammatory mediators can further compromise the BBB and inceased infiltration of inflammatory cells from the periphery to the CNS. Increased inflammatory infiltrates can lead to further neuroinflammation and neuronal injury (Figure 3B). Moreover, levels of some cytokines have been reported to be elevated for months to years following the recovery after SARS-CoV-1 infection (*66*), leading to a post-infectious proinflammatory state that may contribute to a possible long-term neuroinflammation. Nevertheless, advanced investigations are warranted to determine the pathways by which the post-infected brain could contribute to the onset of neuron demyelination or neurodegeneration.

5. Persistent infection of SARS-CoV-2 associated with neurodegeneration

In the following section, we documentated if infection with SRAS-CoV-2 can result in long-term neural damage in both symptomatic and asymptomatic individuals? The first scenario, assumes that neural cells could serve as latent reservoirs for the SRAS-CoV-2. The second one supposes a possible long-term neuroinflammation in the brain. In general, these two possibilities can activate the pathways of apoptosis and oxidative stress leading to neurodegeneration.

In experimental data, viral dissemination in animal brain tissue was shown to be accompanied by vascular endothelium dysfunction, which has been reported to contribute to cognitive impairment (*67*). In addition, susceptible rodent after direct inoculation of HCV-OC43 and SARS-CoV-1 developed acute encephalitis with viral RNA present for several months causing neuronal degeneration (*68*) and ultimately apoptosis (*69*). In fact, Jacomy and his collaborators postulated apoptosis, after CoV infection, as the mechanism involved in neuronal loss observed in the CA1 and CA3 layers of the mice hippocampus (*70*). Also, Chen and Lane assigned apoptosis as a mechanism by which MHV induced neuronal death in mice brain (*71*). Based on these reported results, we suppose that caspases may be the principal executors of apoptotic neuronal cell death as shown in Figure 3C. In fact, caspase-3 has been severally identified as a key mediator of the apoptotic process in neurons (*72*). Noteworthy, alterations in signaling pathways related to apoptosis have been described to be implicated in Alzheimer's disease (AD) (*73*) and Parkinson's disease (PD) (*74*). Hence, SRAS-CoV-2 modulation of neuronal apoptosis both, during latent infections could eventually relate to alterations of neuronal processes leading to neuron degeneration and brain damage.

Oxidative stress is another mechanism by which SRAS-CoV-2 latency infection induces neurodegeneration (Figures 3B and 3C). Viral infection in target cells can induce mitochondrial damage resulting in high ROS generation (*75*). In addition, disruption of tight junction complexes *via* MMPs activation is often associated with enhanced ROS generation (*76*). Notably, recent studies indicate that oxidative stress is associated with neurodegenerative diseases, such as AD (*77*), PD (*74*) and multiple sclerosis (MS) (*78*). For instance,

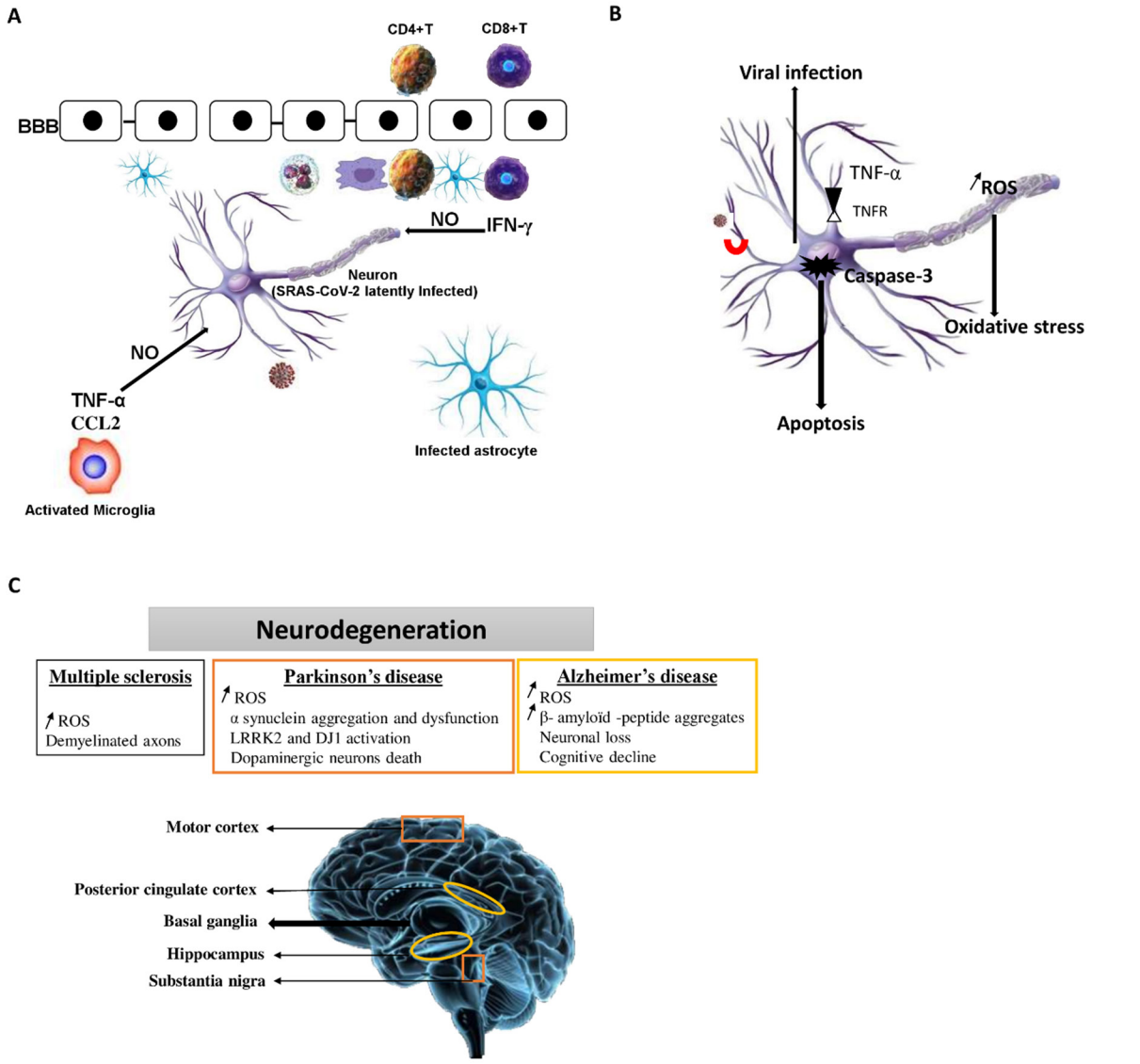

Figure 3. Proposed model of the neurotropism of latent form of SRAS-CoV-2 and its interrelationships with neurodegenerative disorders. **(A)** SRAS-CoV-2 latent brain infection: SRAS-CoV-2 latent form is characterized by the infiltration of $CD8^+$ and $CD4^+$ T cells. Importantly, these T cells are localized near latently infected neurons. In addition, $CD8^+$ T cells can secrete IFN-γ. As a consequence of immune cell infiltration into the brain during persistent SRAS-CoV-2 infection of the brain, cytokines such as TNF-α and IL-1β can affect the BBB, which can exacerbate brain inflammation. **(B)** Synergistic effects between TNF-α and IFN-γ can lead to induced oxidative stress and increased nitric oxide-induced neurodegeneration and demyelination in the brain. In addition, SRAS-CoV-2 modulates cellular processes; latently form of virus hampers events leading to apoptosis at different stages of signaling cascades. **(C)** The boxes show the cellular processes or pathologies that occur in Alzheimer's disease (orange box) or Parkinson's disease (yellow box) or multiple sclerosis (black box) associated with apoptosis, oxidative stress and neuronal injury. Neurodegenerative disease pathologies are expressed in multiple regions of the human and rodent brain, including the motor cortex, posterior cingulate cortex, ventricles and substantia nigra. BBB: blood brain barrier, ROS: reactive oxygen species, ACE2: angiotensin-converting enzyme 2, NO: nitric oxide, TNFR: TNFα receptor.

AD patients overall display increased ROS levels, while a reduced antioxidant capacity (*79*). Importantly, ROS generation is associated with amyloid beta (Aβ)-protein aggregates, which are known to promote synaptic dysfunction (*80*). Also, elevated levels of ROS production associated to demyelination and axonal damage, have been reported in MS (*81*).

5.1. SARS-CoV-2 post-infection associated with multiple sclerosis

Coronaviruses have long been mentioned as potential candidate viruses that could cause or enhance MS disease (*82-85*). Recently, clinical case studies evaluated the prevalence of SRAS-CoV-2 in patients with relapsing-remitting MS (RRMS) comparing it with that of healthy controls (*5,86*). The discovery of CoVs genetic material in the tissue and fluid samples of MS patients has given space for this plausible hypothesis. Indeed, HCV-229E was isolated from the CSF of patient during a first episode of MS (*87*). Before that, HCoV had been isolated from the brain of a patient with MS (*88*). In addition, several experimental models have used CoVs to explore the environmental component triggering the autoimmune

changes in MS (*25,89-90*). For instance, mice infected by MHV3 surviving the initial infection, develop an immune mediated demyelinating disease (*25,91*). Analysis of the spinal cords of infected mice confirms that the loss of myelin integrity is associated with the continued presence of both viral antigen and inflammatory immune cells (*92*), oxidative injury (*93*) and the loss of myeline synthesis (*94,95*). Moroever, in their studies, Savarin *et al*. have reported curtail percentages of $CD4^+$ T cells in the blood of MS patients, which could be associated with impaired responses against CoVs infection (*96,97*). It is possible that defective T cell control due to CoVs infection and exhaustion of T cells in patients with MS may lead to CoVs reactivation in these patients. However, further studies are needed to confirm this hypothesis

5.2. SARS-CoV-2 postinfection associated with Alzheimer's disease

Data in epidemiology and postmortem AD brains have suggested that viral infections may contribute to the onset of AD. For example, CoVs genetic material has been detected in brain samples and found to co-localize with Aβ protein (*98*). Importantly, SRAS-CoV-2 can induce the accumulation of Aβ protein.

In experimental models, HCoV-OC43 induced not only the neuropathogenesis in mice (*70*), but also, an upregulation of a lipocalin apo D protein (*99*). In addition, MHV induced neuroinflammation, exacerbated tau levels, and compromised cognitive function in aged transgenic 3xTg-AD mice (*100*). The inflammation-mediated exacerbation of tau pathological features leads to impairment in cognitive function that is effectively blocked by inhibiting glycogen synthase kinase (GSK)-3β in CA1 neurons of the hippocampus (*100*). Notably, the regions of the CNS damaged during SRAS-CoV-2 are related to the limbic system, composed by subcortical structures and the cerebral cortex that are associated with memory and cognitive processes (Figure 3C). Taken together, these findings suggest that latently form of SRAS-CoV-2 in the brain may induce increased deposition of Aβ in this tissue and accelerating disease development in predisposed patients.

5.3. SARS-CoV-2 postinfection associated with Parkinson's disease

In patients suffering from severe forms of COVID-19, the hypothesis of a systemic failure of the dopamine synthetic pathway should be taken into account and further explored. In fact, the basal ganglia and dopamine-rich brain regions seem to be a vulnerable target to SRAS-CoV-2 (Figure 3C). Consequently, chronic neuroinflammation leads to basal ganglia dysfunction, BBB permeability alteration, and neurodegeneration.

As previously shown, intraperitoneally inoculation of HCoV-OC43 induced microglia activation and neuroinflammation in mice (*101*); followed by encephalitis, neuronal degeneration, and decrease of locomotor activity (*70,101*).

In humans, HCV-OC43 and HCV-229E have been found in the CSF of PD patients (*102*). Of note, intranasal/intraocular inoculation led to detect CoV RNA in the brain, while post-mortem analyses indicated the presence of brain pathology, including inflammation and white matter edema in the basal ganglia (*102*).

In the other hand, neurotropic viruses have been shown to affect the levels of PD-associated proteins, including DJ1 and Leucine rich repeat kinase 2 (LRRK2) (*103*). DJ1 is a gene linked to early onset PD and a key regulator of dopamine and ROS balance in neuronal cells (*74*). Indeed, pathologic LRRK2 and DJ1 activation was found to be an important mediator of neuroinflammation and neuronal damage in *in vitro* and *in vivo* models of neurotropic virus (*103,104*). In addition, Ijomone *et al*. proposed that viral agents from SRAS-CoV-2 can, through microglial activation and oxidative stress, induce the aggregation and oligomerization of α-synuclein in substantia nigra region (*72*).

6. Discussion

This review reported considerable evidences that latent form of SRAS-CoV-2 are associated to adverse outcomes in the brain and induced neurodegenerative's disease. Herein, we highlight the neuroinvasive property of SRAS-CoV-2 and their effect on the brain. Although the exact mechanism of neuroinvasion is still unclear, some penetration routes, such hematogenous route and trans-synaptic transmission, have been suggested. Similarly reported by Zubair *et al*., which also examined the neuropathogenesis and neurologic manifestations of the CoVs in the age of COVID-19 (*19*). Equally important is the demonstration that the long-term effects of COVID-19 seems to be implicated as putative etiologic agents of neurodegenerative diseases (*24,55*).

Moreover, the expression of ACE2 receptors in neurons, astrocytes, and oligodendrocytes contributes to the neurotropism of SRAS-CoV-2 (*19*). Consequently, the persistent infection of SRAS-CoV-2 in the brain could be involved on human neurodegenerative diseases that evolves a gradual process, perhapes, over several decades. Of note, detection of SARS-CoV-1 RNA in the CSF of a patient with SARS has been reported after ten years of infection (*49*).

Considerably, there is an urgent need for longitudinal studies to determine whether the COVID-19 pandemic will lead to enhanced incidence of neurodegenerative disorders in infected individuals. Further studies are needed to confirm these speculations. Therefore, we suggest that a designed cohort study can provide powerful results. In addition, further experiments using in experimental and postmortem studies could provide more informations on the neural alteration and

neurodegeneration after SARS-CoV-2 infection.

Unfortunately, our review is limited to studies published between December 2019 and August 2020, we may have missed some experimental reports of SRAS-CoV-2 virus in association with neurodegenerative's disease. In addition, through our research strategy we focused upon studies that contained both a neuroinvasion and neurotropism of virus, as well as a poor description of neurologic manifestations because, there are currently a small number of published case reports and clinical studies. Third, a diligent documentation of anti-virus therapies is recommended to establish novel therapeutics to target the virus. Currently, there are no specific antiviral agents or vaccines for SRAS-CoV-2 virus. However, some compounds active against SRAS-CoV-2 virus have been reported, including both direct-acting and host-targeting antivirals such as aminoquinolines (*105,106*) and melatonin (*107*); however, most of these compounds have yet to find their way into experimental models and clinical trials. For that, a profound understanding of the tropism and pathogenesis of this virus is imperative for the development of therapeutic design.

Finally, we suggest, through this review, to provide CSF, in part, to better understand the neurotropism of SARS-CoV-2 and to evaluate whether direct (*via* direct infection) or indirect (*via* secondary effects relating to enhanced inflammatory/proinflammatory signaling) impact on the CNS. This goal must be reached using a multidisciplinary approach including brain imaging and tests of brain tissue.

7. Conclusion

This review has highlighted a series of possible additional pathophysiological mechanisms based on some literature data, which elucidate the association between the neurotropism of SRAS-CoV-2 and the development of neurodegenerative's disease. Data from all the above-mentioned studies confirm the neuroinvasive and the neurotropism properties of SRAS-CoV-2 and his effects on the brain. Although the exact mechanism of neuroinvasion is still unclear, two penetration routes (hematogenous route *via* BBB structure and trans-synaptic transmission) of the virus to reach the brain, have been suggested. In fact, virus can modulate numerous key cellular processes in neuron and glia, such as apoptosis and cellular oxidation. Taken together, we suggest that neuron infection with SRAS-CoV-2 can lead to brain damage. These hypothesis call for further studies that evaluate the interrelationship between SRAS-CoV-2 and neurodegeneration. Therefore, we suggest that a designed cohort study can provide powerful results for this possible relationship. In the same way, future challenges in experiments models (*in vitro* and *in vivo*) could shed more light on the possible neural injuries after SARS-CoV-2 infection.

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