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REVIEW

Severe acute respiratory syndrome coronavirus 2 invasion in the central nervous system: a host-virus deadlock

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Summary. – The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) devastation on the central nervous system (CNS) is ascertained by the present clinical findings and the noticeable signs and symptoms. The CNS involvement of the virus is not trivial; although the brain has highly protective systems, the virus has ways to breach them with a destructive potential. For successful entry of the virus, different possible routes with favorable mechanisms are used. The SARS-CoV-2 invasion induces a mechanism of both the innate and adaptive immune response to control virus replication and removal from the CNS tissues. The cytokine storm and autoimmune response during the immunological events result in demyelination, damage of resident cells and neurons, cerebrovascular thrombosis, and dysregulation of neuro signaling pathways. Furthermore, hypoxia and toxemia accelerate the neurological destruction process. The acute attributions on psychology due to inflammation is a hallmark of CNS involved pathogenesis; nevertheless, the productivity, durability, and longevity of virus-specific lymphocytes are the vital indicators for complete removal of viral antigen and in combat against reinfection of the CNS.

Keywords: CNS invasion; immune response; cytokine storm; demyelination; mental status

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Abbreviations: ACE2 = angiotensin-converting enzyme 2; ASC = antibody-secreting cell; BBB = blood brain barrier; BM VECs = brain microvascular endothelial cells; CLN = cervical lymph node; CNS = central nervous system; COVID-19 = coronavirus disease 19; DPP4 = dipeptidyl peptidase 4; MCP = macrophage-chemoattractant protein; MERS-CoV = middle east respiratory syndrome coronavirus; MHC = major histocompatibility complex; MIP = macrophage-inflammatory protein; MMP = matrix metalloproteinase; ORN = olfactory receptor neurons; SARS-CoV(-2) = severe acute respiratory syndrome coronavirus (2); TGF = transforming growth factor; TNF = tumor necrosis factor

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a β-coronavirus of the family *Coronaviridae* (the subfamily *Orthocoronavirinae*, the subgenus *Sarbecovirus*). It is an enveloped and positive sense non-fragmented RNA virus with an average diameter of 100 nm (Wu *et al*., 2020b; Zhu *et al*., 2020). Among the four genera of coronavirus (α-/β-/γ-/δ-coronavirus), the two genera, α-coronavirus and β-coronavirus, tend to infect humans, whereas the others infect birds (Chen *et al*., 2020b; Guo *et al*., 2020). There is a total of seven zoonotic coronaviruses infecting humans, including the latest one, SARS-CoV-2

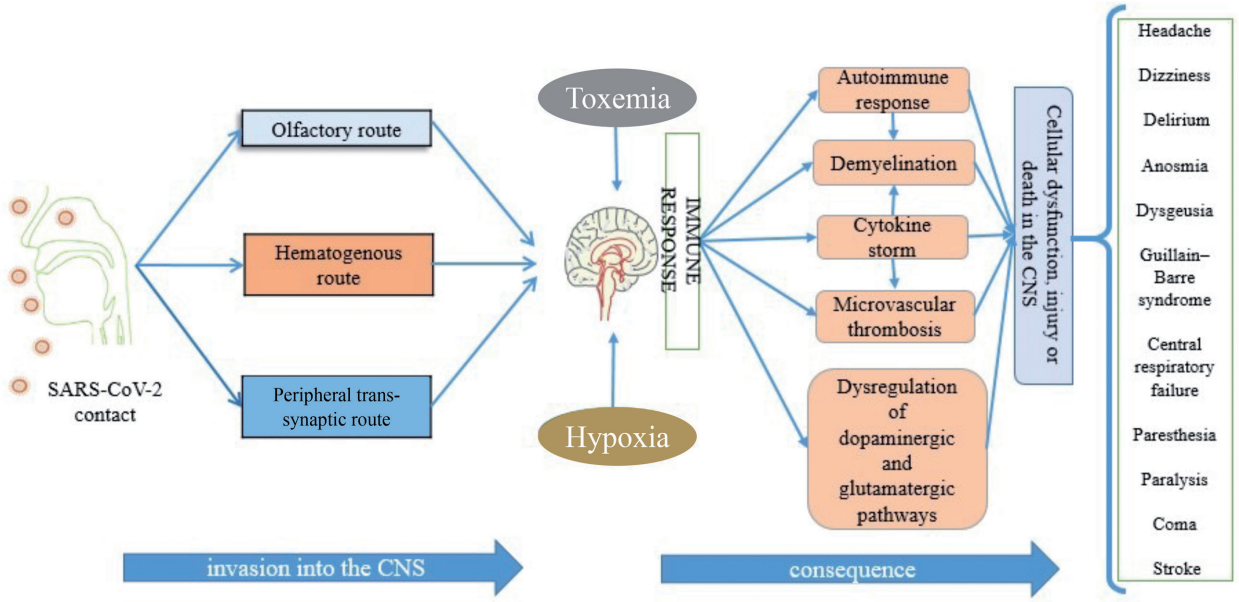


Fig. 1

The figure illustrates an overview of the cascade of events from the SARS-CoV-2 contact to the utmost CNS manifestations upon the virus infection

The first section depicts the three major routes of SARS-CoV-2 CNS invasion: olfactory, hematogenous, and peripheral trans-synaptic route, followed by the immunological response. Conducive factors, toxemia and hypoxia assist the immune response and virus entry. The third section depicts the consequences of virus induced immunological response such as autoimmune response, demyelination, cytokine storm, thrombosis, dopaminergic, and glutamatergic pathway dysregulation, that might lead to cellular dysfunction, injury, or death.

causing coronavirus disease 19 (COVID-19) (Guo *et al.*, 2020). When zoonotic virus resides in the natural host (e.g., bat, rat, pangolin, snake), it does not show any disease symptoms. Still, an incursion into a secondary dead-end host causes mild to severe diseases or even death (Koyuncu *et al.*, 2013).

SARS-CoV-2 is well known for its lower respiratory tract infections, and respiratory failure is the primary cause of the COVID-19 death toll. Besides, it has tremendous worldwide evidence of multi-organ dysfunction and damage (Gavriatopoulou *et al.*, 2020). At present, neurological involvement of this virus has been revealed by the clinical data from infected patients with the cortical and intracranial infection-like symptoms such as headache, anxiety anosmia, and dysgeusia, epilepsy, Guillain-Barré syndrome, disturbed consciousness, encephalitis, and stroke (Gavriatopoulou *et al.*, 2020; Wu *et al.*, 2020b). Initially, from 214 confirmed SARS-CoV-2 cases from 3 hospitals in Wuhan, 36.4% of the patients were reported to have obvious neurological complications (Mao *et al.*, 2020).

When the virus infects the brain and spinal cord neurons, it is challenging to eliminate the virus. As neurons are irreproducible and irreplaceable, T-cell-mediated cytolysis is not conducive to canonic virus clearance (Koyuncu *et al.*, 2013). Few viruses (e. g. herpes zoster, rabies virus) are able to exist in CNS for a long duration with an extensive virus-mediated immunological cytolysis that causes chronic and complex CNS disorders (Johnson *et al.*, 2010; Miller *et al.*, 2016). Therefore, it raises a question, what impact on the CNS can SARS-CoV-2 cause. The putative mechanism on CNS entry based on reported cases of the SARS-CoV-2 infection is not enough to seek for a clear-cut idea on neuropathogenesis to confine neuroinvasion and subsequent complications. This review insights into the SARS-CoV-2 invasion of the CNS, its immunological responses, and consequences it has on humans.

2. The SARS-CoV-2 CNS invasive potential

In the light of contemporary research, SARS-CoV-2 does not always confine to the respiratory system. It has neuroinvasive propensity (Fig. 1) like other coronaviruses, including MERS-CoV, HCoV-229E, and SARS-CoV (Glass *et al.*, 2004; Li *et al.*, 2020b). In fact, SARS-CoV-2 presents an analogous neurotropism to SARS-CoV and MERS-CoV as they have many genetic similarities (Wu *et al.*, 2020a; Zanin *et al.*, 2020). By genome sequencing, researchers

at Beijing Ditan Hospital have detected the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) of the virus-infected patients with clinical encephalitis (Xiang, 2020). Much evidence of cortical lesions in post mortem investigations of the COVID-19 patients might signify its high potential for CNS invasion.

2.1 The CNS invasion vs. BBB

A microenvironment that limits the CNS invasion called the blood brain barrier (BBB) comprises of brain microvascular endothelial cells (BMVECs), astrocytes, pericytes, and the basement membrane. BMVECs, at the CNS vasculature line, have tight junctions, that cannot be found in the vascular system of other tissues or organs (Koyuncu *et al*., 2013). Finger-like projections of astrocytes and pericytes make sheath upon the capillary wall and maintain the BBB's neurovascular functions (Fig. 2b). The basement membrane comprises of an extracellular matrix and surrounds the capillaries. The brain's tight junctions restrict blood-CNS exchange and protect from pathogens (bacteria, viruses, parasites), large molecules such as proteins, hydrophilic molecules, and drugs.

Moreover, perivascular microglia lying between the endothelial and glial cells are engaged in immune surveillance in CNS (Abbott *et al*., 2010). Actually, BBB is the main factor that differentiates the brain from other organs when SARS-CoV-2 involvement in multi-organ disease is in question. Anywise, the barrier preserves this major organ from a fatality of the viral infection.

2. 2 Associated receptor proteins for CNS invasion

The virus's structural proteins, including the nucleocapsid, membrane, envelope, and spike proteins are believed to be involved in immune evasion (Sariol and Perlman, 2020). From the idea of cellular mechanism, it may primarily be agreed that the SARS-CoV-2 invasion into the cell is similar to SARS-CoV due to their 80% genetic similarity (Glebov, 2020). These two viruses probably bind to the same cell membrane receptor protein angiotensin-converting enzyme 2 (ACE2), expressed in human respiratory epithelial and parenchymal cells, small intestine cells, vascular endothelial cells, and kidney cells. Besides, dipeptidyl peptidase 4 (DPP4) is also counted as a point of the virus entry because recent SARS-CoV-2 spike glycoprotein modeling has proposed its interaction with DPP4 (Bassendine *et al*., 2020). DPP4 is expressed on the cell membrane in several organs such as the lower respiratory tract, liver, kidneys, intestine, and the cells of the immune system. DPP4 protein is also associated with the MERS-CoV entry into cells (Boonacker and Van Noorden, 2003; Li *et al*., 2020b). Some studies have shown the direct role of ACE2 in the pathology and virulence of SARS-CoV. As ACE2 regulates renin-angiotensin signaling, the downregulation upon entry and receptor inhibition worsens lung injury (Imai *et al*., 2005).

It was proposed, that ACE2 expressing HeLa cells are susceptible to SARS-CoV-2, whereas non-expressing cells are not (Zhou *et al*., 2020). The host cells and SARS-CoV interaction is mediated mainly through the virus spike protein consisting of subunits S1 and S2, and form homotrimeric spikes on the virus envelope (Gui *et al*., 2017). The binding of spike protein with ACE2 triggers a series of events that lead to the fusion of the virus and host cell membrane, followed by virus entry into the cell. Cryo-electron microscopic observation of the SARS-CoV spike protein and ACE2 receptor interaction, has confirmed that after receptor binding the S1 subunit/ACE2 complex dissociates, conducing S2 transition to a more-stable post-fusion state instead of metastable pre-fusion state. This transition is a vital step of the cell membrane fusion mechanism (Gui *et al*., 2017; Song *et al*., 2018; Zhou *et al*., 2020).

ACE2 receptors are mainly found in spinal neurons and glial cells of the brain. A recent study has analyzed human ACE2 (hACE2) expression in SARS-CoV-2 infected transgenic mice (Bao *et al*., 2020). The SARS-CoV infected hACE2-transgenic mice developed lethal encephalitis (McCray *et al*., 2007). Therefore, it was concluded that the brain is organ susceptible to virus entry, its replication, and neuron damage (Li *et al*., 2020a). The presence of the ACE2 protein on the endothelial cells makes it possible to traverse BBB. However, there is also controversy over ACE2 mediated neuron infection, as they have under normal conditions low expression levels of ACE2. Besides, the presence of the ACE2 is not always enough to predict susceptibility to SARS-CoV-2. Some ACE2-expressing human endothelial and intestinal cell lines are not permissive to SARS-Cov-2 infection (Bernstein *et al*., 2018; Li *et al*., 2020b). However, a study on the spike glycoprotein integrity has revealed that SARS-CoV-2 spike protein has 10 to 20-fold higher affinity than SARS-CoV (Wrapp *et al*., 2020). Collectively, the ACE2 receptor protein might be associated with neuronal uptake mechanism during invasion, although more detailed studies are required.

2. 3 The CNS invasion accelerating factors

After entry of SARS-CoV-2 through the respiratory tract, virus replicates in the alveolar cells of the lungs. The immunological response of that site causes interstitial inflammatory exudation, edema, a permeable membrane, and thrombosis in the pulmonary capillary blood circulation (Guo *et al*., 2020; McGonagle *et al*., 2020). Ultimately, it leads to difficulties in exchanging gas and

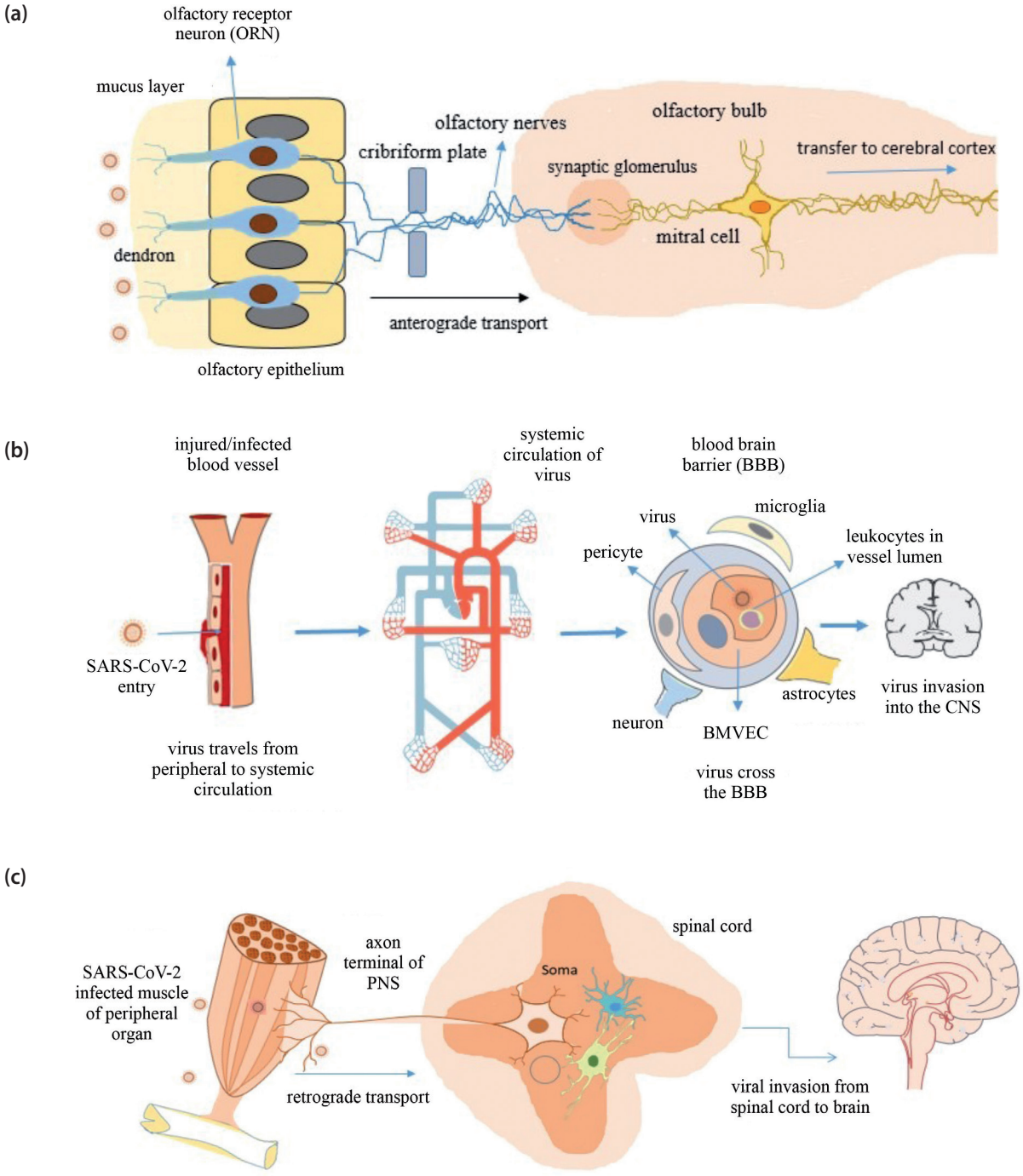


Fig. 2

The three routes of SARS-CoV-2 entry into the CNS

(a) Olfactory route. The virus primarily infects the nasal olfactory epithelium, and then it uses the ORN for anterograde movement along the nerves. In the olfactory bulb, the axon terminal of ORN is connected through a glomerulus structure with the mitral cell dendron terminal. The mitral cell is connected to the anterior olfactory nucleus, olfactory tubercle, olfactory cortex, amygdala, and entorhinal cortex. The virus uses both, anterograde and retrograde transport. **(b)** Hematogenous route. The virus enters the blood stream through the injured peripheral blood vessels. The circulating infected leukocytes will finally reach the cerebral vascular system. The limiting step of CNS entry is to cross BBB, which consists of the brain microvascular endothelium cells (BMVECs) with tight junctions, surrounding basement membrane, pericytes, neurons, and astrocytes. **(c)** The peripheral trans-synaptic route. The virus enters the peripheral neuron, which is directly connected to infected cells of the muscle. By retrograde movement, it reaches the CNS's spinal cord and then spreads to the brain.

lowering the oxygen levels of blood. Hypoxia in the CNS induces anaerobic metabolism of mitochondria (Abdennour *et al*., 2012; Zanin *et al*., 2020). The systemic anabolic metabolites and immunological by-products in the blood resulting from peripheral hypoxia are termed as toxemia. The accumulation of toxic products in CNS due to hypoxia and toxemia causes cerebral vasodilation, intracranial hypertension, and permeability alteration of BBB (Abdennour *et al*., 2012). When this situation continues unabatedly, cerebral circulation related disorders might sharply worsen (Zhang *et al*., 2020). In turn, the hypoxia and toxemia assist in subsequent structural damage and provide higher possibility for the virus to invade the CNS.

3. The routes of CNS invasion

The neurotropic virus exploits its convenient route and mechanism to enter the CNS. SARS-CoV-2 is a respiratory virus, but there is also much evidence of its presence in other organs. The virus gains access into CNS through the trans-synaptic pathway as well as the hematogenous route (Fig. 1 and 2).

3.1 The olfactory route

Trans-olfactory neuroinvasion of the virus is the most prominent and it represents special type of trans-synaptic invasion. SARS-CoV-2 transmission mainly happens through the respiratory tract. Moreover, the nasal cavity has a vulnerable anatomical structure to enable the virus entry. Structurally, the olfactory site's outer layer is a mucus layer protecting chemoreceptor nerve endings. The neuroepithelium consists of limited types of supporting cells and olfactory receptor neurons (ORNs) (Gizurarson, 2012). Unmyelinated axons of neurons enter into the olfactory bulb after penetrating the cribriform plate of the ethmoid bone. The olfactory bulb located on the cerebral hemisphere's inferior side contains mitral cells associated with both anterograde and retrograde neuro-signaling (Fig. 2a). Mitral cells receive the signal through the terminals of ORN (glomerulus structure) and transfer it to the anterior olfactory nucleus, olfactory tubercle, olfactory cortex, amygdala, and entorhinal cortex (Mori, 2015). Furthermore, the high expression of ACE2 on olfactory epithelial support cells of the humans and mice provide evidence of the non-neuronal cell involvement in SARS-CoV-2 entry into CNS (Brann, 2020). Therefore, the virus may invade the olfactory region by both neurons and supporting cells.

A study on a transgenic human ACE2 mice model has shown the olfactory route as the main pathway for the virus entry into the brain. After exposure to SARS-CoV by inhalation, the study detected the virus's presence in the olfactory bulb after sixty hours and in the pyriform cortex and dorsal nucleus after four days (Netland *et al*., 2008). SARS-CoV-2 might infect the trigeminal nerve (a nasal cavity nociceptor) and invade into CNS (Li *et al*., 2020c).

The olfactory route exhibits few unique features in favor of SARS-CoV-2 neuroinvasion into CNS. Firstly, the dendron of ORNs is exposed to the external environment that enables the virus to come into direct contact with the nervous system. Secondly, ORNs have the ability to uptake and transport exogenous substances into the CNS. Thirdly, the olfactory system directly connects to the frontal cortex through the thalamus (Mori, 2015). Finally, the olfactory route overcomes the restriction of invasion imposed by BBB. So, overall, the olfactory route is the most convenient pathway to this virus.

3. 2 The hematogenous route

From the infected cells of peripheral organs (lungs, kidneys, heart, small intestine, testicles), CoV invades the blood vessel's endothelial cells. Then, the virus enters blood circulation by damaging the endothelium. The systemic circulatory virus can be carried by infected leukocytes that induce different immunological responses and release cytokines into the blood. Consequently, it causes several extrapulmonary symptoms. Cytokines are associated with the alteration of endothelial permeability and BBB (Wu *et al*., 2020b). When a virus successfully reaches the cerebral vascular system, it crosses the BBB and ultimately invades the CNS (Fig. 2b). Sometimes, the virus does not infect neurons but infects leukocytes and remains dormant in the circulatory system. Subsequently, this virus can traverse the BBB and enter the brain parenchyma. This mechanism of hiding before the immune defense is called the “Trojan horse” entry (McGavern and Kang, 2011), and SARS-CoV-2 might utilize this strategy (Paniz-Mondolfi *et al*., 2020).

The pulmonary route is the fastest route of virus entry into blood circulation. Type II alveolar epithelial cells, which express high levels of ACE2 protein, are mainly infected by SARS-CoV-2 (Qi *et al*., 2020). The virus binding to ACE2 results in chronological endothelial damage and enters into the systemic circulation and ultimately infects blood cells. Directly, SARS-CoV has been shown to invade human mesenteric root lymph nodes and hilar lymph nodes (Zhao *et al*., 2003). Lymph nodes in the lungs and intestine have a large lymphatic network with the mucosa of eyes, oral tissues, and bronchus (Zhang *et al*., 2010). So, these sites might be infected by SARS-Co-2, and eventually, the virus might gain access to blood circulation through the lymphatic flow.

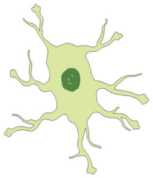
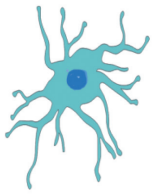
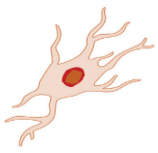
3.3 The peripheral trans-synaptic route

As nerves directly contact all tissues, the peripheral nervous system (PNS) is relatively more attainable to peripheral infections. Contemporary evidence shows that at first, coronavirus may invade PNS from differently affected organs such as lungs, kidneys, intestine, eyes, and liver. Then, the virus replicates and gains access to the CNS through the trans-synaptic route (Li *et al.*, 2020b; Li *et al.*, 2013). Neurons have highly polarized terminals, axons and dendrons that can be separated by long distances. The kinesin and dynein are two families of motor proteins that serve in plus-end-directed anterograde (from the soma to the axon terminus) transport and minus-end-directed retrograde (from axon terminus to soma) transport along microtubules, respectively (Kapitein and Hoogenraad, 2011; Mori, 2015). The virus uses retrograde movement by the post-synaptic pathway to enter CNS (Li *et al.*, 2020c). The neuromuscular junctions might be a gateway to spread SARS-CoV-2 into CNS (Fig. 2c). The three cranial nerves, the facial nerve (VII), the glossopharyngeal nerve (IX), and the vagus nerve (X) convey the smell sense to the nucleus of the solitary tract, and then to thalamic nuclei. The anosmia is a very common symptom in COVID-19 patients (Li *et al.*, 2020c), indicating that the virus might have involvement in this trans-synaptic route to invade the CNS. This pathway avoids the limitations of BBB.

4. Lessons for SARS-CoV-2 infection immune response in CNS from other coronaviruses

During evolution, the human beings achieved well established non-specific and specific immune effector mechanisms to neutralize and eliminate pathogens from infected CNS. An inflammatory response induces release of non-specific soluble effectors to provide an innate antiviral defense against virus invasion. Innate immunity facilitates the development of antigen-specific acquired immunity by establishing persistent immunological memory (Klein *et al.*, 2017). The CNS is mainly composed of two types of cells, namely glial cells and neurons. The glial cells divide into three main types: astrocytes, oligodendrocytes, and microglia (Bergmann *et al.*, 2006). These cells have distinctive heterogeneity in immunological responses that make regional differences in both innate

Table 1. Molecular expression of the glial cells during CoV infection

Glial cell	Chemokine	Cytokine	Other expressed molecules
Astrocyte 	CXCL10[a] CCL5[a, b] MCP-1[b] MCP-3[b] MIP-1β[b] MIP-2[b] MIP-1α[c] MCP-1[c]	TNF-α[c,d,e]; IL-1α[c,e]; IL-1β[c,d,e]; IL-6[c,d]; IL-7[e]; IL-10[c]; IL-12[c]; IL-13[e]; IL-15[e]; IL-16[e]; IL-17[e]; IL-17β[e]; IL18[e]; IFN-α[e]; IFN-β[e]; IFN-γ[c,e]; TGF-β[c]	MHC type I and II antigens[d,f] Type 2 nitric oxide synthase MMP-3[a]
Microglia 	MIP-1α[c] MCP-1[c]	TNF-α[c,d,e]; IL-1α[c]; IL-1β[c,d]; IL-6[c,d,e]; IL-10[c]; IL-12[c]; IFN-α[e]; IFN-β[e]; IFN-γ[c,e]; TGF-β[c]	Integrin alpha X[g] MHC type I and II antigens[f]
Oligodendrocyte 	No information available	IFN-α[h] IFN-β[h]	MHC type I antigens MMP-12[a]

MCP, macrophage-chemo attractant protein; MIP, macrophage-inflammatory protein; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; TGF, transforming growth factor; MHC, major histocompatibility complex; MMP, matrix metalloproteinase. [a](Bergmann *et al.*, 2006); [b](Lane *et al.*, 1998); [c](Edwards *et al.*, 2000); [d](Sun *et al.*, 1995); [e](Lavi and Cong, 2020); [f](Suzumura *et al.*, 1986); [g](Templeton *et al.*, 2008); [h](Li *et al.*, 2010).

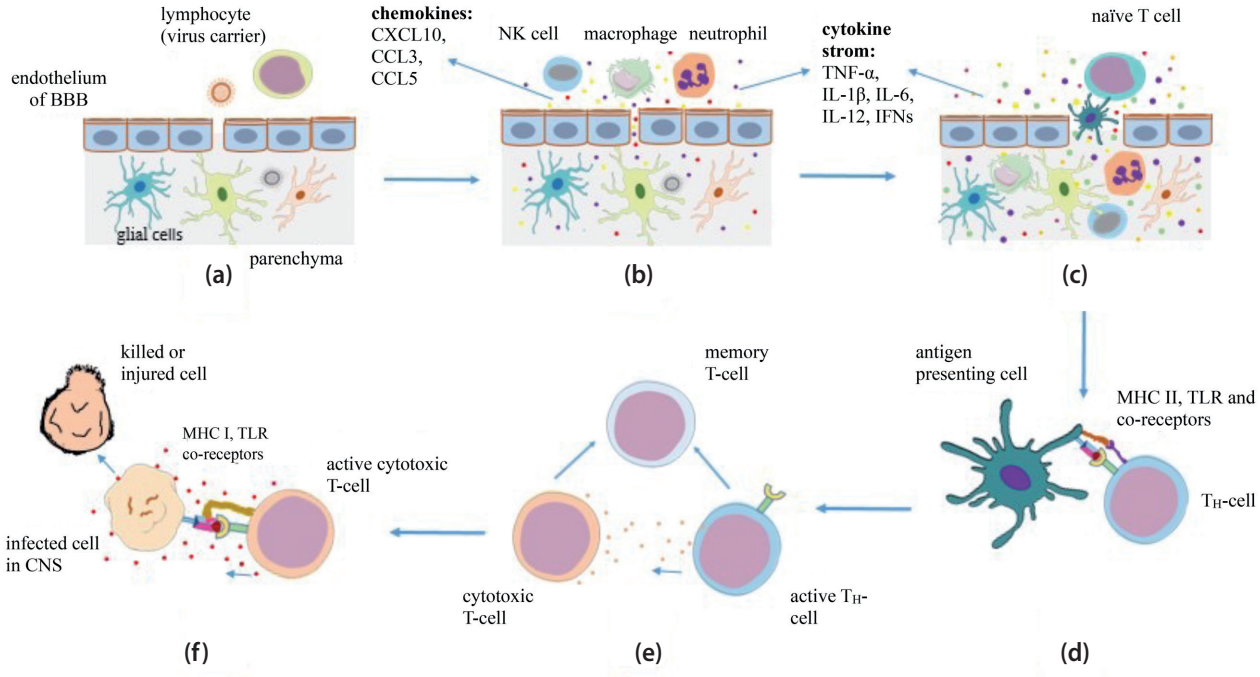


Fig. 3

Overview of innate and adaptive cell-mediated immune response in the CNS during coronavirus infection
Upon the viral invasion, the endothelial cell's tight junctions are disrupted and the virus and immune cells can cross the BBB **(a)**. Infected parenchymal glial cells release chemokines and cytokines that attract macrophages, neutrophils, NK cells. Along with resident cells of CNS, immune cells release cytokines **(b)**. The release of tremendous amount of pro-inflammatory cytokines that induce strong inflammatory response is called cytokine storm **(b, c)**. At the same time, naive T-helper cells (CD4+) are activated in the cervical lymph node by antigen-presenting cells **(d)**. Active T_H cells release Th1 cytokine to induce maturation and activation of cytotoxic T-cells (CD8+) **(e)**. Both can keep memory T-cells in the clonal expansion **(e)**. The infected cells in CNS present the MHC type I antigen that is recognized by the T_C cells. These immune cells release cytolytic molecules (e. g. granzyme B), and consequently, kill or injure the infected cells **(f)**.

and adaptive immunity (Table 1). The SARS-CoV-2 is a new virus and was identified nine months ago. So far, the research on the molecular, cellular, and immunological basis of the virus is at the beginning. Meanwhile, researchers are trying to correlate the immunological patterns of SARS-CoV-2 with other coronaviruses based on current CNS manifestations and clinical data.

4.1 Innate immune response in CNS

The invasion of the virus into CNS induces a cascade of events expressing chemokines, pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and a tissue inhibitors of MMPs (TIMP-1) (Bergmann *et al.*, 2006). At the initial step, the virus-infected and uninfected glial cells release chemokines CXCL10, CCL3, and CCL5 (Fig. 3b). Indirectly, the molecules disrupt BBB and infiltrate immune cells such as macrophages, neutrophils, and natural killer cells (NK), which release inflammatory factors (Fig. 3c). The expression of MMP is also associated with cytokine release, inflammatory cell influx into CNS, and cellular damage of CNS (Bongetta *et al.*, 2020; Yong *et al.*, 2001).

The chemokines and pro-inflammatory cytokines involved in SARS and MERS infection are CXCL10, CCL2, CCL3, IL-6, and TNF (Chen *et al.*, 2020a; Yang *et al.*, 2020). Murine hepatitis virus (MHV) infection in CNS also induces the release of CXCL10 and CCL3 (Lane *et al.*, 2000). CXCL10 transmits the signal through CXCR3 to recruit NK cells (Trifilo *et al.*, 2004). At the same time, astrocytes and microglia predominantly produce TNF-α, IL-1α, IL-1β, IL-6, and IL-12 (Table 1). This cytokine secretion is, in general, not pathogen- or cell-specific. The pleiotropic cytokine IL-6 induction prompts inflammatory cells to cross BBB. Studies showed that TNF-α, IL-12, and IL-1β mRNA levels were also increased, even when inflammation was absent (Bergmann *et al.*, 2006; Rempel *et al.*, 2005). Despite having a minor role in the activation of NK cells, their secreted IFN-γ might upregulate MHC class I and class II molecules to facilitate antigen presentation. CCL3 might recruit and stimulate T-cells to promote adaptive immunity. The largest innate immune response components are the

macrophages accumulated by CCL5 activity (Bergmann *et al*., 2006).

The type I interferon expression pattern by the CNS resident cells is similar to all viral infections (Salazar-Mather *et al*., 2002). Coronaviruses involve a strategic way to keep off detection by pattern recognition receptors or they block pathways of IFN signaling (Sariol and Perlman, 2020). The virus can delay or dysregulate the response of IFN and take a chance of invading the body. In SARS-CoV infection, the virus successfully evokes this evasion strategy because infected monocytes/macrophages and dendritic cells do not release type I IFN (Law *et al*., 2005). *In vivo* studies on SARS-CoV-2 have revealed that IFN pretreatment is sensitive, but patients' inflammatory response is impaired, producing low levels of IFN with low signaling (Blanco-Melo *et al*., 2020; Lokugamage *et al*., 2020).

4.2 Adaptive immune response in CNS

4.2.1 Cell-mediated response

During the early virus replication, antigens from ependymal cell layer enter the cervical lymph nodes (CLN) via CSF, whereas naïve T-cells are activated and by chemokines directed into the CNS (Klein *et al*., 2017). As an innate immune component, monocytes are recruited into the CNS, and by differentiation converted into antigen-presenting cells (APC) – macrophages or dendritic cells. Otherwise, APCs might acquire the antigens in CNS and then enter into the CLN. Dendritic cells or macrophages in CLN present antigen, and subsequently lead to virus-specific T-cells (both CD8+ and CD4+) activation and expansion (Greter *et al*., 2005). The memory T-cells can easily activate at reinfection (Fig. 3d,e). Though the direct activity of helper T-cells (T_H) is unclear, it has a role in cytotoxic T-cell (T_C) survival as well as function. The T_H-cell mediated action on T_C is somehow unknown but may be relied upon T_H 1 cytokines that help T_C-cells maturation and activation (Santin *et al*., 2000). During acute infection, the virus-specific memory T-cells control virus replication with better efficiency than activated T-cells (Bergmann *et al*., 2006).

Two major cytokines CXCL9 and CXCL10, attract activated NK and T-cells, which express CXCR3. When T-cells (both T_H and T_C) accumulate in the brain, neutrophils and NK cells' counts decline. Yet, T-cell-produced IFN-γ maintains the macrophage persistence with higher MHC class II expression (Chen *et al*., 2005). The accumulation of the virus-specific T-cells causes a concomitant decline of the virus load. These cells also modulate the most of the immunological markers except the chemoattractants of T-cells, CXCL10 and CCL5 (Lane *et al*., 1998). The chemoattractants sustain T-cell recruitment and IFN-γ expression. At the same time, pro-inflammatory cytokine (e. g. IFN-β IL-1α, IL-1β, IL-6, IL-12) levels remain in low levels (Parra *et al*., 1997), although virus-specific T-cells produce TNF-α.

By the time the T-cell accumulation peaks, most of the T_C and T_H cells show the virus specificity in CNS (Bergmann *et al*., 1999). In the systemic immune response, the SARS-CoV infected mice model has shown that T-cells alone are effective to partly control the infection (Zhao *et al*., 2009). A study on 522 COVID-19 patients has demonstrated that the counts of total T-cells, T_H cells, and T_C cells were less than 800, 400, and 300/μl, respectively, negatively correlating with patients' survival (Diao *et al*., 2020).

The peak of IFN-γ secreted from virus-specific T_C-cells coincides with the T-cell count in CNS that indicates its role in T-cell infiltration. Virus-specific T_C cells expressing granzyme B, a serine protease, have an efficient cytolytic effect (Fig. 3f) (Ramakrishna *et al*., 2004). In the CNS, the T_C cell-mediated cytolytic mechanism is completely cell-type dependent. Viral replication in microglia and astrocytes is uncontrolled in perforin deficient mice but not in oligodendrocytes. However, the mice with competent perforin mediated cytolytic activity for IFN-γ deficiency are efficient in controlling the virus in microglia and astrocytes but not oligodendrocytes (Lin *et al*., 1997). So, it indicates the role of IFN-γ signaling in oligodendrocyte infection control, which is also proved by the signaling defect in these cells in infected mice. Fas/FasL cytolytic pathway does not show any important role in the pathogenesis (Parra *et al*., 2000). Still, it may be required during virus clearance when perforin-mediated cytotoxicity has expired.

4.2.2 Humoral immune response

The humoral adaptive immune response is slower than the cell-mediated response. The cytolytic activity of CoV specific T_C cells is lost after the 14th day post-infection (Ramakrishna *et al*., 2004), paid off by humoral immunity to prevent viral recrudescence into CNS. The JMHV infected $IgM^{-/-}$ and syngeneic C57BL/6 mice have exhibited clinical disease progression and recovery, after the acute phase in CNS, respectively (Lin *et al*., 1999). However, the virus-specific antibodies were proved to prevent virus reactivation even in B lymphocyte deficient mice (Ramakrishna *et al*., 2003). All that assures the crucial role of humoral immunity to eliminate viral persistence and recrudescence in CNS.

Antibody secreting cells (ASC) (B lymphocytes) activation and differentiation occurs in CLN or spleen. ASCs then migrate into CNS parenchyma. Concurrent evidence demonstrates that the induction of humoral response in CNS is highly dynamic characterized by naive B cells, IgM^+, and IgA^+ plasma cell recruitment, which

is gradually replaced by IgG^+ plasma cells (Phares *et al.*, 2013). The virus-specific ASCs continue to accumulate in CNS until three months of post-infection. At this time, the ASCs persist at a higher level than virus-specific T cells (Tschen *et al.*, 2002). However, the transport of antibodies into parenchyma attenuating BBB's integrity harms CNS invasion protection (Zhou *et al.*, 2002). What is more, antibodies in coronavirus infection can interact with the neuron's myelin sheath that causes demyelinating encephalomyelitis (Zimprich *et al.*, 1991). Therefore, the humoral response has both positive and negative sides in viral clearance from CNS.

5. The consequences of SARS-CoV-2 CNS invasion

Viruses in the *Coronaviridae* family are neurotropic and cause neurological complications like encephalopathy, polyneuropathy, demyelinating lesions, and ischemic stroke (Cao *et al.*, 2020; Kim *et al.*, 2017). Recent research on COVID-19 confirmed cases showed multifactorial neurological findings indicating potential ability of the virus to invade CNS. Very common neurological complications of COVID-19 patients are headache, dizziness, delirium, anosmia and dysgeusia, Guillain–Barre syndrome, central respiratory failure, acute necrotizing hemorrhagic encephalopathy, stroke, and neuropsychiatric symptoms (Fig. 1) (Jasti *et al.*, 2020; Wu *et al.*, 2020b). A study over the online portal on 125 patients who met the clinician's definitions of the clinical case in the United Kingdom has shown that 77 patients presented with a cerebrovascular event, of whom 57 got an ischemic stroke, 9 suffered an intracerebral hemorrhage and 1 CNS vasculitis. Moreover, 39 out of 125 patients had altered mental status. Among them, 9 had unspecified encephalopathy and 7 encephalitis. Twenty-one patients were diagnosed with a new pattern of psychological status change. However, six patients presented dementia-like neurocognitive syndrome (Varatharaj *et al.*, 2020). Now, there are other countless case studies on the neurological manifestation of COVID-19 patients.

The pathogenesis in viral infections is directly conjoined to the immunological response that presents as systemic inflammatory response syndrome (SIRS) (Chen *et al.*, 2020a). At pro-inflammatory state, SARS-CoV-2 infection induces a cytokine storm (Yang *et al.*, 2020). A study has shown that *in vitro* CoV-infected, primary glial cells secrete many cytokines such as IL-6, IL-12, IL-15, and TNF-α (Table 1). The sustained release of the cytokines like IL-1, IL-6, and TNF-α by immune cells, is responsible for glial cell activation, but it has a subsequent demyelinating impact on neurons (Bohmwald *et al.*, 2018; Mehta *et al.*, 2020). Antibody-mediated demyelination is also observed in CNS's persistent immune response (Zimprich *et al.*, 1991). However, the virus triggers a mechanism to produce toxic chemicals against glial cells. This is a possible alternative way of demyelination as well as cellular damage (Zanin *et al.*, 2020). MRI has shown lesions in the periventricular white matter, bulbo-medullary junction, and both the cervical and dorsal spinal cord, indicating the demyelination effect of SARS-CoV-2 (Zanin *et al.*, 2020). Encephalitis is another noticeable manifestation of SARS-CoV-2 infection in the brain (Xiang, 2020). Brain parenchyma is vulnerable to inflammatory lesions caused by the virus, which is the main reason behind encephalitis. This lesion is also characterized by several acute onset symptoms like headaches, vomiting, fever (mild to severe), convulsions, and unconsciousness (Ellul and Solomon, 2018). Encephalitis is a life-threatening clinical condition that may occur even in the absence of any type of respiratory symptoms (Morvan, 2020).

Furthermore, toxic encephalopathy is another consequence of viral infection caused by the accumulation of toxic products with clinical conditions like systemic hypoxia and toxemia (Fig. 1). This consequence is characterized by a mild symptoms (headache, dysphoria, delirium, mental disorder) or severe symptoms (disorientation, paralysis, loss of consciousness, coma) (Dobbs, 2011). Hypoxia and viremia have been detected during SARS-CoV-2 infection, and that is the potential cause of toxic encephalitis of the patients. Almost 40% of SARS-CoV-2 infected patients symptomize the conditions by headache, disturbed consciousness, and other brain dysfunctions (Guo *et al.*, 2020; Mao *et al.*, 2020). Due to toxic encephalitis and inflammatory reaction, the fluid infusion reaches the ventricles and subarachnoid space that may cause cerebral edema with symptoms like headache, unconsciousness, disorientation, and mental change status. Several studies have revealed edema in the brain tissue of COVID-19 patients (Xu *et al.*, 2020). Excessive expression of chemokines and cytokines modulate the synthesis and function of different neurotransmitters in the brain, and as a consequence, it changes the functional activity of the patients. Two noteworthy neurotransmitters are involved (Fig. 1): dopamine is associated with memory, motivation, and reward, and glutamate associated with learning and memory formation (Klein *et al.*, 2017). Therefore, the behavioral and emotional change of COVID-19 patients may lie behind the pathways modulation due to immune response. SARS-CoV-2 triggers an autoimmune response that may lead to demyelination and axonal damage to the brain's residence cells. Guillain Barré syndrome (GBS) and Miller Fisher syndrome result from an autoimmune response (Dalakas, 2020; Gutierrez-Ortiz *et al.*, 2020). There is a correlation between coagulation and inflammation. Dysregulation of pro-inflammatory (e.g. IL-6) and pro-

coagulative factors (e.g. fibrinogen) due to endothelial damage result in cerebral microvascular thrombosis that blocks blood circulation into the brain parenchyma, and it causes cell death due to oxygen insufficiency. Ultimately, COVID-19 patients can have an ischemic stroke (Benger *et al*., 2020; Connors and Levy, 2020). Systemic thromboembolism also affects the mental status in which thoughts and emotions are severely impaired (Mongan *et al*., 2020). The olfactory and gustatory dysfunctions are characterized by anosmia and dysgeusia, with 41% and 38.2% patients, respectively (Agyeman *et al*., 2020). The olfactory nerve, the facial nerve, the glossopharyngeal nerve, the vagus nerve, and their associated centers or regions in CNS damage or injury leads to aforementioned complications.

6. Summary and future perspective

The interaction between SARS-CoV-2 and its human host is noteworthy in many ways. This virus was proved to cause multi-organ involvement with mild to severe complications. The neurological complications are very common in the COVID-19 confirmed cases that allege the CNS invasive potential of the SARS-CoV-2. The virus uses its spike protein to interact with ACE2 located on the nerve membrane. The successful CNS invasion is coordinated with several factors, including the route of entry, the host immune response against the virus, and blood circulation related features that maintain BBB's integrity. The olfactory site is a most "comfortable" route of entry into the CNS. Upon brain invasion of SARS-CoV-2, the heterogeneity of cerebral parenchymal cells results in a substantive immune response. The response makes both protective and destructive consequences on the human beings. As a protective response, immune cells endeavor to eliminate the virus. On the other hand, the destructive consequence is characterized by different neurological complications, including headache, dizziness, seizures, consciousness disorder, paresthesia, paralysis, coma, ischemic stroke, and other pathopsychological signs.

The putative mechanism of the SARS-CoV-2 neuroinvasion and immune response based on the other viruses of the same family is not sufficient to understand the viral neuropathology. As the CNS controls and coordinates the peripheral organs' functions, CNS involvement is the main cause of this pandemic's high lethality. Precise investigations on the CNS invasion, immune response, and consequence on a molecular to cellular basis might help to determine the proper protective measures to minimize the complications and lethality. Urgent studies on the chemokine and cytokine expression patterns, protein expression on immune and CNS resident cells, structural features of the viral antigen unit, cell-mediated and humoral virus elimination process in the CNS should be the strategic tools for neuroprotection using the existing drugs in the market to cope with the current pandemic. The studies mentioned above will have implications for developing novel immunotherapies and designing vaccines safe for the CNS.

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