



Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Neurotropism of SARS-CoV-2 and its neuropathological alterations: Similarities with other coronaviruses

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ARTICLE INFO

Keywords:

COVID-19

Coronavirus

Neuropathological alterations

Nervous system

ABSTRACT

A novel coronavirus (SARS-CoV-2) emerged from Wuhan, China, and spread quickly around the world. In addition to fever, cough and shortness of breath, it was confirmed that the patients also have manifestations towards the central nervous system (CNS), especially those critically ill ones. In this review, we will discuss how SARS-CoV-2 gain access to the CNS and the possible consequences. Both SARS-CoV-2 and SARS-CoV-1 in 2002 share the same receptor angiotensin-converting enzyme 2 (ACE2), which can be found in the brain and mediate the disease process. Both direct attack of SARS-CoV-2 and the abnormal immune response in the CNS would contribute to the disease. Also, there is a relationship between SARS-CoV-2 and the occurrence of acute cerebrovascular diseases.

1. Introduction

In December 2019, there was an outbreak of pneumonia of unknown etiology in Wuhan, Hubei province in China, which was subsequently identified as a new-type coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously 2019-nCoV) (Lu et al., 2020). The infection moved rapidly through China with thousands of people infected and has then spread around the world, posing a threat to global health. The infection induced by SARS-CoV-2 (COVID-19) is associated with the development of acute respiratory distress syndrome (ARDS) with high rates of mortality (Huang et al., 2020a), although symptoms could be mild in some cases. Patients who have comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, hypertension, and malignancy are predisposed to poorer clinical outcomes, while a greater number of comorbidities correlated with worse condition in COVID-19 (Guan et al., 2020). Common symptoms at the onset of the illness are fever, dry cough and fatigue. However, there are also many patients presented initially with neurological symptoms, such as headache, dizziness, and myalgia (Chen et al., 2020a; Huang et al., 2020b; Wang et al., 2020). Other neurological manifestations also

include central nervous system (CNS) manifestations (impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and neuralgia), skeletal muscular injury manifestations (Liu et al., 2020b; Mao et al., 2020), and neuropsychiatric disorders (Varatharaj et al., 2020). Thus, it would be of utmost importance to explore the role of the virus in nervous system to aid in guiding more efficient treatment.

Coronaviruses (CoV) are enveloped, single positive stranded RNA viruses that can infect a variety of species of mammals and birds (Arbour et al., 2000; Perlman and Netland, 2009). There are four genera of CoV within the Coronavirinae subfamily: AlphaCoV (ACoV), BetaCoV (BCoV), DeltaCoV (DCoV) and GammaCoV (GCoV) on the basis of their phylogenetic relationships and genomic structures (Adams et al., 2017; Andrewes, 1952; Cui et al., 2019). The ACoV and BCoV infect only mammals, and usually cause respiratory diseases in humans and gastroenteritis in animals which can pose a heavy burden on livestock diseases (Cui et al., 2019). Bats are the gene source of ACoV and BCoV, and avians are the gene source of DCoV and GCoV. The bat CoV may jump from bat to other mammals, including humans, while the bird CoV

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<https://doi.org/10.1016/j.neubiorev.2020.10.012>

Received 12 May 2020; Received in revised form 16 September 2020; Accepted 12 October 2020

Available online 19 October 2020

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may jump from avian to some mammalian species, such as whale and pig, leading to interspecies transmission (Woo et al., 2012). Currently, seven coronaviruses were described as pathogenic in humans, called human coronavirus (HCoV): HCoV-OC43, HCoV-229E (Myint, 1995), the severe acute respiratory syndrome coronavirus (SARS-CoV, here referred to as SARS-CoV-1) (Drosten et al., 2003), HCoV-NL63 (van der Hoek et al., 2004v), HCoV-HKU1 (Woo et al., 2005; Zaki et al., 2012), the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2. The three highly pathogenic viruses that resulted in outbreaks amongst humans, SARS-CoV-1, SARS-CoV-2 and MERS-CoV, all belong to the BCoV genus and can cause severe respiratory syndrome in humans (Su et al., 2016; Zhou et al., 2020a). Specially, the emerging SARS-CoV-2 share 79.5 % sequence identify to SARS-CoV-1, and the seven conserved replicas domains in ORF1ab used for CoV species classification are 94.6 % amino acid sequence identical to SARS-CoV-1, suggesting the two belong to same species (Zhou et al., 2020b). Presumably, SARS-CoV-1 was produced by recombination in bats, and then transmitted to farmed civets or another mammal, where it acquired further mutations before spillover to humans (Cui et al., 2019). The intermediate host for MERS-CoV is dromedary camel (de Wit et al., 2016) and for SARS-CoV-2 being not yet determined.

In addition to systemic and respiratory symptoms, neurological invasion has been demonstrated in all three epidemics (Wu et al., 2020). HCoV-OC43, 229E were also reported to have the ability to infect the CNS (Arbour et al., 2000, 1999a, 1999b; Xu et al., 2005). Although the exact role of SARS-CoV-2 in nervous system is poorly understood, it is expected to be similar to SARS-CoV-1 and other coronaviruses described over the years. This article focuses on the neurotropism of HCoV, possible mechanisms of neuroinvasion, and the possible neuropathology and neuropathogenesis in SARS-CoV-2 infection. We will also review the role of the virus in the development of cerebrovascular diseases.

2. Neurotropism of HCoV

HCoVs are known as circulating pathogens worldwide among the human population that infect human upper respiratory tract, mostly causing common cold (Gerna et al., 2007; Regamey et al., 2008; Vabret et al., 2008). However, viruses can reach the lower respiratory tract to cause bronchitis, pneumonia, COPD exacerbation (Linden et al., 2019; Myint, 1995; Talbot and Falsey, 2010), or even spread to extra-respiratory organs including the CNS in more vulnerable individuals (Desforges et al., 2019). Some HCoVs (HCoV-OC43, NL63, HKU1) frequently cause benign upper respiratory infections in healthy children (Dijkman et al., 2012). However, HCoV-OC43 were found in a child with acute disseminated encephalomyelitis (ADEM) (Yeh et al., 2004), and in another child suffering severe combined immunodeficiency with encephalitis (Morfopoulou et al., 2016). Both HCoV-229E and HCoV-OC43 are involved in the pathogenesis of multiple sclerosis and Parkinson's disease (Arbour et al., 1999a, 2000; Desforges et al., 2014; Fazzini et al., 1992; Murray et al., 1992; Salmi et al., 1982; Stewart et al., 1992). They have the capacity to infect human astrocytes and microglia in primary cultures (Bonavia et al., 1997) and can persist in human neural-cell lines (Arbour et al., 1999a, 1999b). SARS-CoV-1 has also been proved to have neuroinvasive properties. The neurological complications reported include peripheral nervous diseases, rhabdomyolysis, neuromuscular disorders and large artery ischemic stroke (Chao et al., 2003; Tsai et al., 2004; Umaphathi et al., 2004; Wang et al., 2003), similar to that of COVID-19. It is documented that viral RNA can be detected in the brain (Gu et al., 2005; Xu et al., 2005). By using RT-PCR, SARS-CoV-1 genomic sequences have been detected in cerebral spinal fluid (CSF) (Hung et al., 2003). A SARS coronavirus strain was isolated from a brain tissue specimen obtained from a patient with significant CNS manifestations, which confirmed viral infection of neurons (Xu et al., 2005). Patients infected with MERS-CoV also experienced neurologic symptoms, such as seizures, headaches and confusion (Saad et al., 2014). Besides, three cases including suspected ADEM,

encephalitis, and stroke were reported (Arabi et al., 2015), as well as four cases including 3 cases of Guillain-Barre syndrome (GBS) and a case of Bickerstaff encephalitis (Kim et al., 2017). Although not recognized by the authors, one patient's brain MRI images were highly suggestive of acute hemorrhagic necrotizing encephalopathy (AHNE), a condition recently reported during the outbreak of COVID-19 epidemic in the USA (Arabi et al., 2015; Poyiadji et al., 2020; Román et al., 2020). The neurological complications did not coincide with respiratory symptoms, but emerged 2–3 weeks later (Kim et al., 2017). However, although murine models develop CNS infection following intranasal inoculation with MERS-CoV, this virus has never been detected in the CNS of humans (Li et al., 2016).

The neurotropism of SARS-CoV-2 has already been well documented in many articles (Aghagoli et al., 2020; Fotuhi et al., 2020; Liu et al., 2020a; Politi et al., 2020; Román et al., 2020; von Weyhern et al., 2020v; Whittaker et al., 2020) since its outbreak in December 2019. In a report of a 25-year-old female with COVID-19, the brain MRI images showed significant cortical hyperintensity in the right gyrus rectus, suggesting viral infection (Politi et al., 2020). The autopsies of six fatal cases found significant CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage, which was not attributed clinically relevant COVID-19-related severe hypoxia (von Weyhern et al., 2020). A few reports of possible meningitis or encephalitis associated with COVID-19 showed SARS-CoV-2 in the CSF or brain (Huang et al., 2020a; Moriguchi et al., 2020; Novi et al., 2020; Zhou et al., 2020a). However, the virus was not detected in the CSF from other cases (Garg et al., 2020; Ye et al., 2020). The authors speculated that the virus spread transiently in the CSF and is accompanied by a strong inflammatory response (Ye et al., 2020). Notably, several studies have successfully demonstrated the presence of anti-SARS-CoV-2 antibodies in the CSF, such as antibodies against S1 protein, S2 protein, envelop proteins and nucleoprotein (Benamer et al., 2020; Lu et al., 2005). The anti-SARS-CoV-2 antibodies in the CSF may also serve as an indicator of CNS involvement in patients with COVID-19 (Cheruiyot et al., 2020). Frontal lobe tissues from postmortem examinations of a patient infected with SARS-CoV-2 were analyzed by electronic microscopy. The virus was detected in neural and capillary endothelial cells, which provided direct evidence of SARS-CoV-2 in human brain tissues (Baig et al., 2020).

3. Neuronal ACE2 receptor recognition by SARS-CoV-2

CoV possesses 4 or 5 genes encoding structural proteins (S, E, M, N; HE for the genus β -coronavirus), and several genes encoding nonstructural proteins (Desforges et al., 2013). The spike protein (S) recognizes cellular receptor and mediates the entry of coronavirus into host cells by first binding to the host receptor and then fusing virus into host membranes (Bosch et al., 2003; Li, 2016; Spaan et al., 1988). SARS-CoV-1 uses S protein receptor-binding domain (RBD), which contains all of the structural information for host receptor binding (Li, 2005), to specifically recognize its host receptor angiotensin-converting enzyme 2 (ACE2) (Li, 2015; Li et al., 2003). S protein exhibits the domain organization of class I fusion proteins, which require proteolytic activation by host cell enzymes (Eckert and Kim, 2001). Proteolytic cleavage of the viral envelope glycoprotein into a receptor binding and a fusogenic transmembrane subunit is also important to regulate viral entry and infectivity (Nagai, 1993). Members of type II transmembrane serine proteases (TTSP)-transmembrane protease serine 2 (TMPRSS2) and human airway tryptase (HAT), as well as cathepsin L in target cells have been found to cleave and activate the S protein (Bertram et al., 2011; Glowacka et al., 2011; Simmons et al., 2013, 2005) in SARS. Similarly, the 2019 SARS-CoV-2 is also considered to use ACE2 as a receptor for entry into host cells (Letko and Munster, 2020; Wan et al., 2020; Zhou et al., 2020b). A recent study showed that SARS-CoV-2 was able to use ACE2 as an entry receptor in HeLa cells expressing ACE2 protein, but not in cells without ACE2 expression (Zhou et al., 2020a). 2019-nCoV-S may use the cellular protease TMPRSS2 for priming (Hoffmann et al., 2020),

which may be associated with the virus transmission and infectivity (Meng et al., 2020).

ACE2 is a carboxy-peptidase responsible for the formation of vaso-dilatory peptides such as angiotensin-(1-7) (Ang1-7) (Donoghue et al., 2000; Ferrario, 2006; Vickers et al., 2002). This causes endothelial-dependent vasodilation mediated by nitric oxide release through receptor Mas, and is responsible for the regulation of heart function and blood pressure (Boehm and Nabel, 2002; Sampaio et al., 2007; Santos et al., 2003). ACE2 mRNA is present not only in alveolar epithelial cells, but also in renal, cardiovascular tissues and tissues from gastrointestinal like colon (Harmer et al., 2002). These are consistent with symptoms of lung, kidney, heart and other multiple organ damage in many critical patients (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020). In addition, ACE2 is expressed widely throughout the CNS (Chen et al., 2020; Zubair et al., 2020). A recent report analyzed the expression of ACE2 in the brain from publicly available brain transcriptome databases. In spatial distribution analysis, ACE2 was expressed relatively high in the substantia nigra and brain ventricles. In Cell-type distribution analysis, ACE2 was expressed in many neurons, astrocytes and oligodendrocytes in human middle temporal gyrus and posterior cingulate cortex, but not in the prefrontal cortex and rarely in the hippocampus (Chen et al., 2020). This study also demonstrated similar expression patterns in mouse brain. In other murine models, ACE2 expression has been identified in the motor cortex, cytoplasm of neurons, glial cells, and sympathetic pathways in the brainstem (Doobay et al., 2007; Zubair et al., 2020). The presence of ACE2 receptors in neural cells appears to be critical for the neurotropism of this coronavirus using protein S. Remarkably, a recent study characterized the ultrastructure of SARS-CoV-2 by high-resolution cryo-electron microscopy, and found that the S protein has a higher affinity for ACE2 than SARS-CoV-1 (Wrapp et al., 2020), which indicates SARS-CoV-2 may have higher neuroinvasive potential compared with previous CoVs (Natoli et al., 2020).

4. Possible mechanisms of viral neuroinvasion

There are two possible mechanisms how HCoV penetrate the CNS (Bohmwald et al., 2018; Desforges et al., 2019, 2014, 2013). The first one is the hematogenous route, which is the infection of the endothelium or the “Trojan Horse” mechanism (Bohmwald et al., 2018; McGavern and Kang, 2011). The blood-brain barrier (BBB) is composed of brain microvascular endothelium cells (BMECs), pericytes, astrocytes and extracellular matrix. Different immune cells interact with the BBB to mediate immunity at this barrier site, such as perivascular macrophages and resident microglia (Daneman, 2013; McGavern and Kang, 2011). The BMECs are held together by tight junctions (TJs) that limit the movement of molecules and ions between cells (paracellular). Lack of fenestra and extremely low rates of pinocytosis/transcytosis also limit the movement of molecules through the cell (transcellular) (Daneman, 2013). Innate immune cells such as macrophages and dendritic cells are also found in the meninges and choroid plexus, enabling surveillance of fluid spaces (McGavern and Kang, 2011). Because of these structures, viruses can hardly infect the brain through the blood in an immune competent host with a fully functional BBB (Berth, 2009). However, in a state of immunosuppression, both direct viral infection of endothelial cells and the local production of inflammatory mediators in the CNS could lead to the disruption of the BBB (Aghagoli et al., 2020). ACE2 receptors are expressed in endothelial cells throughout the body including lung, heart, kidney, intestines, as well as brain (Hamming et al., 2004), which provides an opportunity for virus inside the bloodstream to transport across BMECs and pericytes via endocytotic vesicles, or directly across the BBB via infected endothelial cells. Post-mortem analysis of three patients with COVID-19 revealed viral inclusion structures in endothelial cells by electron microscopy and endotheliitis by histological analyses (Varga et al., 2020), providing evidence for direct viral infection of endothelial cells accompanied by

accumulation of mononuclear inflammatory cells (Román et al., 2020). Another report also detected SARS-CoV-2 viral particles in endothelial cells of frontal lobe brain sections from postmortem examinations of COVID-19 patients. Electron microscopic imaging even demonstrated endocytosis or exocytosis of viral particles across endothelial cells, indicating a hematogenous route for viral infection of the CNS (Paniz-Mondolfi et al., 2020).

The destabilization of TJs can result in disruption of BBB permeability, which allows viral entry into the brain in a paracellular transmigration way (Bohmwald et al., 2018). For example, the virus-induced chemokine monocyte chemoattractant protein-1 (MCP-1, CCL2) can contribute to the increased BBB permeability by causing alterations of TJ proteins in endothelial cells, mainly through the CCR2 receptor (Stamatovic et al., 2005). Actually, it has been proved that systemic inflammation, whether of bacterial, viral, or toxic origin, can compromise BBB (Sankowski et al., 2015; Steardo et al., 2020). SARS-CoV-2 infection triggers a massive storm of systemic inflammation in some patients (Liu et al., 2020), and the massive release of cytokines, chemokines, and other inflammatory signals can lead to significant breaks in the BBB, providing an opportunity for the virus to enter the CNS via blood flow (Steardo et al., 2020). Viruses may also first infect leucocytes-mainly monocytes/macrophages, and then traffic into the brain via a paracellular route, termed the Trojan horse mechanism (Bohmwald et al., 2018; Koyuncu et al., 2013; McGavern and Kang, 2011). This mechanism has been well described in human immunodeficiency virus (HIV) and some other viruses, that the virus in the bloodstream is carried to the brain through infected immune cells that penetrate the BBB (Kim et al., 2003; Santiago-Tirado and Doering, 2017). In COVID-19 patients, ACE2 expression was detected on both lymph node-associated CD68+ macrophages and tissue-resident CD169+ macrophages (Chen et al., 2020e; Sokolowska et al., 2020). Moreover, autopsied spleens and lymph nodes were observed to be directly infected by SARS-CoV-2 (Chen et al., 2020e). It is tempting to speculate whether SARS-CoV-2, similar to HIV, has evolved to use macrophages as a Trojan horse for CNS infection. In addition, animal experiments have shown that viruses may enter the nervous system through the circumventricular organs (Bentivoglio et al., 2018) that normally lack a blood-brain barrier (BBB), or through dorsal root ganglia and autonomic (including cardiac) ganglia (Li et al., 2012), neither of which have got blood-nerve barrier (BNB), providing another way for viral neuroinvasion (Román et al., 2020).

The second route of HCoV transmission to the CNS is through axonal transport and transneuronal spread from olfactory and trigeminal nerve endings in the nasal epithelium or the sensory fibers of the vagus nerve (Berth, 2009; Koyuncu et al., 2013; Román et al., 2020). Viruses can enter the PNS by direct fusion with or penetration to the plasma membrane of the nerve endings, or by endocytosis. They bind to receptors that mediate their entry. Then they undergo efficient retrograde transport to the cell body using motor proteins where the viral DNA is instilled in the nucleus, and spread retrograde along nerve synapses, then eventually gain access to the CNS (Koyuncu et al., 2013; Zubair et al., 2020). Specially, CoVs can be transmitted from airway mechanoreceptors and chemoreceptors to the medullary cardio-respiratory centers through a synapse-connected route proved by experiments (Desforges et al., 2019; Román et al., 2020), which may be partially responsible for the acute respiratory failure of infected patients (Li et al., 2020b).

Some viruses can also invade the olfactory epithelium and olfactory neurons (Barnett and Perlman, 1993; Koyuncu et al., 2013; Perlman et al., 1990). Olfactory neuroepithelium consists of a limited number of cell types arranged in a roughly laminar pattern, with sustentacular cells in the most apical location, followed by olfactory receptor neurons (ORNs) and then the basal. Mature ORNs are bipolar sensory receptors whose apical dendrites terminate in the olfactory epithelium at the roof of the nasal-pharyngeal cavity, while the unmyelinated axons leave the neuroepithelium and penetrate the cribriform plate into the olfactory

bulb (OB). The olfactory system forms direct connections to the frontal cortex without thalamic relay (Mori et al., 2005). Usually, OB is effective in clearing viruses and controlling their entry and replication due to its innate immune response to viral infection of the CNS (Durrant et al., 2016). However, some viruses are still able to enter CNS through the olfactory route (Mori et al., 2005). Experimental intranasal infection of HCoV-OC43 in susceptible mice has confirmed this route of infection, which presents a magnification of infected ORN and viral dissemination in the brain from OB to the brainstem (Desforgues et al., 2019; St-Jean et al., 2004). Another study used SARS-CoV-1 infected mice that are transgenic for human ACE2 placed under control of the cytokeratin 18 promoter (K18-hACE2), to show that the virus enters through the olfactory nerve with subsequent transneuronal spread (Netland et al., 2008). Since such transneuronal spread could not support the infection of other regions, such as those brainstem nuclei that are not directly connected to the olfactory bulb, the authors assumed that once the virus was established in the brain, it might spread along specific neurotransmitter pathways or through non-neuronal routes (blood or Virchow-Robin space) (Natoli et al., 2020; Netland et al., 2008). Early olfactory dysfunction, a unique clinical manifestation of certain SARS-CoV-2 infected patients (Giacomelli et al., 2020; Lechien et al., 2020), indicated the early viral invasion of the nervous system via the olfactory bulb. Additionally, a recent report described a SARS-CoV-2-infected patient with mild respiratory symptoms and acute anosmia. On the fourth day of symptoms, MRI showed bilateral hyperintensity of the olfactory bulbs and of the right gyrus rectus on fluid-attenuated inversion recovery (FLAIR) sequence (Politi et al., 2020), which further supports the hypothesis of the olfactory pathway (Aghagholi et al., 2020). However, another study in mouse and human datasets found that two key genes involved in SARS-CoV-2 entry, ACE2 and TMPRSS2, were expressed in olfactory epithelial support cells and stem cells, as well as nasal airway epithelial cells, but not in olfactory sensory neurons (Brann et al., 2020). These findings may question the olfactory bulb as an entry pathway for SARS-CoV-2 into the CNS (Natoli et al., 2020).

5. Postulated SARS-CoV-2 associated neuropathology and neuropathogenesis

The most common feature of the CNS in patients with COVID-19 was headache, followed by impaired consciousness, agitation or delirium, and seizures (Román et al., 2020; Zubair et al., 2020). These symptoms may be caused by critical illness-related encephalopathy, or they could be specific to SARS-CoV-2 infection (Helms et al., 2020). Many HCoVs may reach the CNS and induce different types of encephalopathy, including encephalitis (Jacomy and Talbot, 2003; Morfopoulou et al., 2016; Yeh et al., 2004), and other long-term neurological disorders. Autopsies from SARS-CoV-1 cases showed edema and degeneration of neurons (Gu et al., 2005; Gu and Korteweg, 2007), as well as necrosis and broad hyperplasia of glial cells (Xu et al., 2005), which were also found in COVID-19 patients (Wei, 2020). In HCoV-OC43 infected mice, neurons underwent vacuolation and degeneration (Jacomy and Talbot, 2003). Strong microglial reactivity and inflammatory reactions were also seen in infected regions (Jacomy and Talbot, 2003). Recently, a study of 18 SARS-CoV-2 autopsies reported that all had acute hypoxic injury in the cerebrum and cerebellum, with neuronal loss in the cortex, hippocampus, and cerebellar Purkinje cell layer, but no thrombi or vasculitis (Solomon et al., 2020). The presence of ACE2 in the neuron provides a possibility for SARS-CoV-2 to gain access to the CNS where it causes associated pathological changes. The pathogenesis of neuronal damage is caused either by direct virus effects or by immunopathology (Bohmwald et al., 2018; Desforgues et al., 2019, 2014).

Under normal circumstances, the BBB determines the number and nature of leukocytes permitted to enter the CNS. In addition, the lack of distinct lymphatics and identifiable resident dendritic cells, as well as the low level of immunoglobulins and adhesion molecules required for

interaction between leukocytes and CNS, contribute to a quiescent resting state in the healthy brain (Bergmann et al., 2006; Hickey, 2001). Once viruses reach the CNS through the two routes mentioned above, the surrounding microglia are activated, and start to phagocytose cellular debris which accumulates as a result of virus-induced cytopathogenic effects. Then comes T lymphocytes, which restrict viral replication in microglia and astrocytes on CD8 + T-cell perforin-mediated cytotoxicity, allowing the secretion of more chemotactic and toxic substances. The secretion of the soluble mediator, interferon- γ , controls viral replication in oligodendrocytes (Bergmann et al., 2006). Moreover, CD4 + T cells play an important role in accelerating CNS inflammation and demyelination, possibly by regulating RANTES (a C-C chemokine) expression, which in turn coordinates the trafficking of macrophages into the CNS, leading to myelin destruction (Lane et al., 2000). In order to avoid harmful responses to itself, the CNS immune system are regulated by distinct subsets of regulatory CD4+ and CD8 + T cells as well as NK T cells that could limit overactive immune response (Belkaid and Rouse, 2005). In some cases, failure to eliminate virus may lead to a state of virus–host coexistence and the persistence of infection (Bergmann et al., 2006).

Both injury to immune cells and abnormal immune responses may contribute to the pathogenesis of virus-induced neurological diseases. COVID-19 reduces counts of peripheral lymphocytes (Liu et al., 2020b; Wang et al., 2020; Xu et al., 2020), similar to that previously observed in SARS (Cui et al., 2003; Gu et al., 2005; Gu and Korteweg, 2007; Xu et al., 2005), though the mechanisms of lymphopenia remain unclear. SARS also causes deficiencies in the innate immune response (Cheung et al., 2005; Law et al., 2005; Nicholls et al., 2006), since the infected dendritic cells showed low expression of antiviral cytokines (interferon α [IFN- α], IFN- β , IFN- γ , and interleukin 12p40 [IL-12p40]) (Desforgues et al., 2013; Law et al., 2005). Lymphocyte counts were lower for COVID-19 patients with CNS complications than those without CNS complications, which indicates more suppressed immune response, especially in the severe subgroup (Mao et al., 2020). Damage to the immune system is associated with insufficient virus elimination. For example, depletion of microglia is essential for infection with mouse hepatitis virus (MHV) -a neurotropic coronavirus (Wheeler et al., 2018), and leads to neuronal damage and apoptosis. In acute encephalitis, viral replication in the brain causes destructive lesions of the gray matter (Rupprecht et al., 2002; Shoji et al., 2002; Talbot et al., 2011). In addition, neurofilament phosphorylation can be found in those cells, an outcome of viral replication (Desforgues et al., 2014). SARS-CoV-1-infected K18-hACE2 mice died prior to a significant infiltration of immune cells in the CNS, which also supported this notion that direct viral infection contributes to the CNS dysfunction (McCray et al., 2007). These pathogens show toxicity to neurons and cause cell death by inducing the programmed cell death (PCD) (Carmen et al., 2009; Desforgues et al., 2014; Favreau et al., 2012, 2009). Various pathways and cellular factors are involved during HCoV-OC43-induced PCD of infected neurons, such as calcium overload, endoplasmic reticulum (ER) stress, excitotoxicity, poly(ADP-ribose) polymerase (PARP) activation, calpain and oxidative stress related to the formation of reactive oxygen species (ROS) involved in mitochondrial dysfunction, which eventually cause neurodegeneration and neuronal cell death (Desforgues et al., 2014). HCoV-OC43 infection of human neurons induces the unfolded-protein response and caspase-3 activation, and causes cell death while the viral S glycoprotein is involved in the process (Favreau et al., 2009). However, the mitochondrial apoptosis-inducing factor (AIF) and cyclophilin D (CypD) are main factors in HCoV-OC43-induced PCD, while caspases seem not to be essential (Favreau et al., 2012). Glutamate is synthesized by neurons and released in the synaptic cleft as an excitatory neurotransmitter. It may lead to neuronal degeneration and eventual cell death through an excitotoxic process (Mark et al., 2001). Not surprisingly, the virus-induced pathological process appears to be linked to the glutamate excitotoxic mechanism (Brison et al., 2011; Carmen et al., 2009; Desforgues et al., 2014). Also, viruses may induce an acute but clinically

silent infection followed by a persistent infection that interferes with functions of neural cells (Giraudon and Bernard, 2010; Oldstone et al., 1982) without the production of viral particles.

Viruses can damage the CNS and cause neurologic manifestations not only due to viral replication in brain cells but also the misdirected immune response of the host (Giraudon and Bernard, 2010; Koyuncu et al., 2013; Xu et al., 2005). The infiltrated immune cells, mainly astrocytes and microglia (Li et al., 2004), could produce inflammatory mediators such as proinflammatory cytokines and matrix metalloproteinases (MMPs), which finally result in a severe state of brain inflammation that further contributes to neuropathogenesis (Edwards et al., 2000; Giraudon and Bernard, 2010). Infection of the human astrocytic cell line by HCoV-OC43 caused an upregulation of IL-6, TNF- α , and MCP-1 mRNA expression. This virus also modulated the activity of MMP-2 and -9, and in both human astrocytic cells and microglial cells augmented nitric oxide production which is a non-specific inflammatory mediator of oligodendrocyte death (Edwards et al., 2000). TNF- α and MCP-1 are main factors to disrupt tight junctions of the BBB, playing a role in the increased vascular permeability and leukocyte migration associated with a number of neurological diseases, such as HIV encephalitis, Alzheimer's disease, and ischemic stroke (Becker, 2001; Halliday et al., 2000; Langford and Masliah, 2006; Mark and Miller, 1999; Stamatovic et al., 2005). TNF- α also acts as a known trigger of apoptosis. It may contribute to the apoptosis of uninfected cells, as well as the infiltration and activation of microglia (Robertson et al., 2001). High level of proinflammatory cytokines and chemokines could be detected in infected brains by SARS-CoV-1 of transgenic mice that express the SARS-CoV-1 receptor ACE2 (hACE2) (McCray et al., 2007). Chemokine induced by IFN- γ (CXCL9, a CXC chemokines family member), expressed in gliocytes with the attracted infiltration of CD68+ monocytes/macrophages and CD3+ T lymphocytes in the brain mesenchyme, was involved in the brain immunopathology of the SARS-CoV-1 invasion (Xu et al., 2005). The chemokine has been reported to participate in host defense and immune damage by attracting activated T cells, NK cells, and monocytes that express CXCR3 (Liu et al., 2001; Xu et al., 2005). MHV spike glycoprotein is regarded as a major determinant of neurovirulence, which is responsible for the extensive viral spread in both neurons and astrocytes (Phillips et al., 2002). It also mediates a massive influx of lymphocytes into the brain with a large proportion of CD8+ T cells (Phillips et al., 2002). This is one of the possible factors for the demyelination disease caused by MHV (Matthews et al., 2002). Similarly, HCoV-OC43 induces immune cell infiltration and cytokine production in the CNS of mice. Variants of point mutations in the viral S protein which was reproducibly acquired during viral persistence in human neural cell cultures result in drastically modified neuropathology, characterized by flaccid paralysis and demyelination (Jacomy et al., 2010; St-Jean et al., 2006). Compared to wild-type virus, the modified neuropathology induced by the mutant virus was associated with increased viral spread and significantly increased T-lymphocyte infiltration into the CNS, as well as significantly increased level of pro-inflammatory cytokines and chemokines (Jacomy et al., 2010; St-Jean et al., 2006). Antibodies have been found in the CSF of patients with COVID-19, which have been shown to activate macrophages, resulting in their migration into the CSF and ultimately in demyelination (Kim and Perlman, 2005). The virus is thought to have antigenic determinants similar to those present in human neuronal cells. The immunological response to SARS-CoV-2 cross-reacts with the myelin autoantigens, leading to postinfectious encephalomyelitis known as an autoimmune demyelinating disease of the brain, such as ADEM, and identified in patients with COVID-19 (Garg et al., 2020; Parsons et al., 2020).

In the COVID-19 epidemic, patients with comorbidities are prone to a cytokine storm. Some patients have an abrupt onset of cytokine storm that stems from an intense inflammatory response against the virus. Cytokine storm, which is characterized by the overproduction of proinflammatory cytokines and chemokines, is considered to be the

main cause of ARDS and multiple organ dysfunction that can lead to hypoxia/metabolic changes, and subsequently result in diffuse brain dysfunction (Garg et al., 2020). This is consistent with the fact that COVID-19 encephalopathy appears to be more common in patients with evidence of multiple organ dysfunction and elevated markers of systemic inflammation (Cummings et al., 2020; Helms et al., 2020; Korallnik and Tyler, 2020; Scullen et al., 2020). Cytokines can also be directly neurotoxic, mediating CNS cell damage, alone or in concert, through their mediated disruption of the BBB in the absence of direct viral spread or invasion (Aghagholi et al., 2020; Allan and Rothwell, 2001). For example, AHNE, a rare encephalopathy usually associated with viral infection, was observed in a patient with COVID-19. It was thought to be possibly mediated by cytokine toxicity (Poyiadji et al., 2020). Neuroinflammation coupled with prolonged hypoxia may promote acute and chronic neuropsychiatric developments and cognitive impairment (Stearo et al., 2020). In recent years, neuroinflammation has been recognized to be associated with psychiatric disorders such as schizophrenia, autism spectrum disorder, bipolar disorder and depression. Common pathways include microglial activation, pro-inflammatory cytokines, molecular mimicry, anti-neuronal autoantibodies, self-reactive T cells, and disturbance of the BBB (Pape et al., 2019). Not surprisingly, a UK study found that among 125 patients diagnosed with COVID-19, 39 (31 %) had altered mental status (defined as acute changes in personality, behavior, cognition, or consciousness), and they were usually young patients. Among them, 9 (23 %) had unidentified encephalopathy, 7 (18 %) had encephalitis, and 23 (59 %) fulfilled the clinical case definitions for psychiatric diagnoses as classified by the notifying psychiatrist or neuropsychiatrist (Varatharaj et al., 2020). Old patients recovering from respiratory symptoms are at risk of long-term delirium or deficits in attention and memory (Troyer et al., 2020). This is clearly due to persistent, uncontrolled neuroinflammation induced by systemic inflammation under prolonged hypoxia conditions, which result in damage to hippocampus and cortical areas associated with altered cognitive functions and behavior (Sasannejad et al., 2019; Steardo et al., 2020).

Studies published so far suggest that neurological involvement in the pathogenesis of SARS-CoV-2 does seem to be associated with a more "severe" infection and subsequent mortality. However, at present, the direct cause and effect of the deterioration of the nervous system in patients with SARS-CoV-2 has not been attributed to the virus itself, and the relationship could also be explained by association with other multi-organ system failures. The direct impact of this "neurological involvement" on mortality and morbidity remains to be elucidated (Whittaker et al., 2020).

6. Acute cerebrovascular diseases in patients with COVID-19

Small or large thrombi can be seen in the brain and multiple other organs in a significant number of COVID-19 patients (Fotuhi et al., 2020). Old patients are more likely to develop acute cerebrovascular diseases, which may be associated with the higher D-dimer level found in severe patients than that of non-severe ones (Chen et al., 2020; Li et al., 2020a; Mao et al., 2020; Wang et al., 2020). High level of D-dimer is thought to be associated with the hypercoagulable state observed in patients with COVID-19, predisposing to thrombosis (Jose and Manuel, 2020). Another possible mechanism is that the binding of SARS-CoV-2 with ACE2 receptor may result in the down-regulation of ACE2 in human, thus breaking the balance between ACE/Ang II/AT1R pathway and ACE2/Ang (1-7)/Mas receptor pathway in the renin-angiotensin system (RAS) (Sun et al., 2020), which has been described in SARS-CoV-1 infection (Imai et al., 2008). The imbalance results in vascular dysfunction which is the leading cause of atherosclerosis, cardiovascular disease (CVD) and hypertension (Gibbons, 1997). The activation of RAS may also cause abnormally high blood pressure in hypertensive patients with COVID-19, increasing the risk of cerebral hemorrhage. CNS hemorrhage is a fatal complication of COVID-19 in

patients younger than 65 years old according to a study (von Weyhern et al., 2020). In addition, intravenous immunoglobulin (IVIg) and corticosteroids have been widely used in critical patients. The use of IVIg may contribute to the pro-thrombotic state in the patients. IVIg infusion can induce the formation of immune complexes, increase platelet aggregation and finally increase blood viscosity, leading to thrombosis, although it is believed that IVIg-induced increase in viscosity may only be consequential in patients with hypercoagulable states (Dalakas and Clark, 2003; Okuda et al., 2003). Also, it seems that combined therapy of IVIg and corticosteroids would play a synergistic role in thrombosis development (Feuillet et al., 2004). Virus-induced inflammation of the vessel wall at the base of the brain is believed to be responsible for stroke with many viruses such as varicella zoster virus (VZV) and HIV (Chow et al., 2011). Also, the systemic vasculitis has been found in SARS patients at autopsy (Ding et al., 2003). SARS-CoV-2 could also attack human blood vessels and lead to vasospasm or thrombosis by its binding to ACE2 receptors in endothelial cells since the virus has been demonstrated within endothelial cells (Varga et al., 2020). Virus-induced systemic vascular endotheliitis promotes vasoconstriction, edema and a pro-coagulant state (Bonetti et al., 2003), which is of great significance for stroke. Acute VZV infection itself may induce a transient, immune-mediated pro-thrombotic state (Chow et al., 2011), which may happen in SARS-CoV-2 as well. High number of platelets and prolonged prothrombin time in critical patients of COVID-19 may be high risk factors for acute cerebrovascular events (Chen et al., 2020; Wang et al., 2020). Cardiac dysfunction and significant hypotension caused by the virus in critical patients are also a risk. The link between the virus and acute cerebrovascular diseases seems to be multifaceted, so the management of critical patients with COVID-19 needs careful planning. For example, the prophylactic administration of anticoagulation such as low molecular weight heparin could decrease thrombotic complications. When IVIg is used for treatment, a slow infusion rate should be advocated (Orbach et al., 2005) and its combination with corticosteroids should be used with caution (Feuillet et al., 2004).

7. Conclusions

The outbreak of COVID-19 has spread around the world with more and more countries involved. Apart from symptoms of respiratory system, many neurologic manifestations are seen especially in those with severe infections, which may be associated with a poor prognosis. Since there are a proportion of patients presented initially with atypical neurological symptoms, it is important for physicians to differentiate and screen patients for proper treatment. The presence of coronavirus in the human central nervous system is widely known over the past decades, and it may cause potential neuropathological consequences in susceptible individuals. SARS-CoV-2 may get into the brain through the hematogenous route or neuronal dissemination. ACE2 present in neurons permits the virus to interact with cells. Possible mechanisms for virus to attack the CNS include deficiencies in the innate immune response, direct infection of immune cells, dysregulation of cytokines/chemokines, autoimmunity and direct viral cytopathic effects of neurons. Acute cerebrovascular events are also major complications among hospitalized patients. Compared with common patients, they have the most critical condition, older age and more underlying diseases. Hemodynamic changes in the course of the disease are more pronounced with the use of intravenous immunoglobulin, cardiogenic shock, and possible vasculitis. Last, we should not ignore the possibility that SARS-CoV-2 invades the CNS leading to persistent infection in the brain.

Declaration of Competing Interest

None.

Acknowledgements

This study was supported by the Liaoning Revitalization Talents Program, China, 2018 and the Cultivating Discipline Support Plan of China Medical University, China, 2019.

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