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Neurological involvement of COVID-19: from neuroinvasion and neuroimmune crosstalk to long-term consequences

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Abstract: As the coronavirus disease 2019 (COVID-19) pandemic continues to be a multidimensional threat to humanity, more evidence of neurological involvement associated with it has emerged. Neuroimmune interaction may prove to be important not only in the pathogenesis of neurological manifestations but also to prevent systemic hyperinflammation. In this review, we summarize reports of COVID-19 cases with neurological involvement, followed by discussion of possible routes of entry, immune responses against coronavirus infection in the central nervous system and mechanisms of nerve degeneration due to viral infection and immune responses. Possible mechanisms for neuroprotection and virus-associated neurological consequences are also discussed.

Keywords: immune response; nerve degeneration; neuroprotection; neurotropism; SARS-CoV-2.

Introduction

Since the first case was reported in Wuhan, China, in December 2019, the global pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection or coronavirus disease 2019 (COVID-19) is still ongoing in more than 200 countries. Although the mortality rate of SARS-CoV-2 is lower compared to the previous outbreak-causing coronaviruses, i.e., SARS-CoV and Middle East respiratory syndrome (MERS)-CoV (Petrosillo et al. 2020), SARS-CoV-2 is more easily transmitted. In March 2020, the number of cases started to exponentially increase

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worldwide. As of the writing of this manuscript, the World Health Organization (WHO) database (WHO 2020b) recorded more than 42 million cases with more than 1.1 million fatalities. The main symptoms of the disease are dry cough, fever, dyspnea and later, severely infected patients may die from respiratory failure, myocardial injury, shock or kidney failure (Sardu et al. 2020). Most of the severe cases are related to the patients' dysregulated immune function; i.e., unsuccessful viral clearance followed by an overwhelming "cytokine storm" that leads to systemic inflammation and organ damage which may involve hemoglobinopathy and coagulopathy (Henry et al. 2020).

Besides the common respiratory symptoms, growing attention to neurological manifestations of COVID-19 has emerged. A report from Wuhan, the first epicenter of the COVID-19 outbreak, recorded neurological symptoms in 36.4% of patients. The symptoms are more common (45.5%) in patients with severe respiratory symptoms (Mao et al. 2020). As of the writing of this manuscript, there were more than a dozen reports, short reviews, commentaries, letters to editor and editorials in several medical journals that addressed this issue (Ahmad and Rathore 2020; Conde Cardona et al. 2020; Das et al. 2020). Those reports helped to increase awareness among neurologists (Jin et al. 2020; Sellner et al. 2020), since early recognition is beneficial in order to manage the cases properly and avoid further transmissions. Most of the publications provide only short highlights to the problem of accurate identification, due to the urgency for information-sharing during the pandemic situation.

The highly infectious capacity of SARS-CoV-2, due to several amino acid differences in its Spike 2 (S2) protein compared to SARS-CoV, has been described (Xia et al. 2020). Beside the cells of the respiratory tract, the receptors of SARS-CoV-2, Angiotensin Converting Enzyme (ACE)-2, are expressed in other tissues including nervous tissue (Doobay et al. 2007; Gowrisankar and Clark 2016; Hamming et al. 2004). However, the expression of transmembrane protease, serine 2 (TMPRSS2) that is required for S protein priming is not fully documented. Without the cellular protease, SARS-CoV-2 cannot enter the cellular cytoplasm. Another surface molecule that belongs to immunoglobulin super family, CD147 or basigin has been

reported to be a SARS-CoV-2 receptor (Wang et al. 2020). It is widely expressed in epithelial, neuronal, myeloid and lymphoid cells (Grass and Toole 2015), hence the increase of the likelihood of infection in multiple organs.

Reports of neurological symptoms could be found during the previous SARS-CoV and MERS-CoV epidemics (Arabi et al. 2015; Hwang, 2006) as well as the endemic coronavirus strains OC43 and 229E (Desforges et al. 2019). A recent review indicated that the related animal-targeted coronavirus strains may induce nervous tissue damage and some of them have been utilized in the development of animal models for neurological diseases such as multiple sclerosis (MS) (Natoli et al. 2020). Accordingly, the chance of the nervous tissue involvement of SARS-CoV-2 pathology is high. The damage of the brain, the regulator of the body's homeostasis, may contribute to the pathology of other organs during the course of COVID-19. Observations that most of the patients that need intensive care could not breathe spontaneously suggest the loss of involuntary control of breathing from the central nervous system (CNS), resulting in respiratory insufficiency (Li et al. 2020a).

Key findings suggest that immune responses play a significant role in COVID-19 pathogenesis (Huang et al. 2020; Mehta et al. 2020; Qin et al. 2020). SARS-CoV-2 infection can activate innate and adaptive immune responses (Ong et al. 2020; Wilk et al. 2020). However, uncontrolled inflammatory innate responses and impaired adaptive immune responses upon virus infection may lead to harmful tissue damage, both locally and systemically (Cui et al. 2020; Giamarellos-Bourboulis et al. 2020; Xu et al. 2020). As a result, there is a high chance of immune response involvement in neurological manifestations of COVID-19.

In this review, we elaborate the possible routes of infection into the nervous system, immune responses in the nervous system against the virus and its involvement in nerve tissue damage. We also discuss some suggestions of modalities correlated to neuroprotection and therapy. In the end, the possibility that nervous tissue may be involved in the long-term consequences in the survivors of SARS-CoV-2 infection is discussed. We searched publications from PubMed, Google Scholar and WHO databases. However, the latest publications are yet to be peer-reviewed. By summarizing data from current research progress, previous outbreaks and animal models infected with coronavirus and other neurotropic viruses, we may learn the possible mechanisms behind the current observation of nervous tissue involvement in SARS-CoV-2 pathogenesis. Furthermore, we may become more aware of the consequences of the SARS-CoV-2 infection in the nervous system of the survivors.

Reported neurological symptoms

Loss of sense of smell (anosmia) and taste (ageusia) were self-reported by 75%-85% (Lechien et al. 2020; Yan et al. 2020) of patients with COVID-19, who may not have had nasal obstruction or rhinorrhea. The phenomena are more prominent in female than male patients (Lechien et al. 2020). However, other data revealed the occurrence of the symptoms in less than 19% (Aggarwal et al. 2020b) or even as low as 5% (Mao et al. 2020) of the patients. The cause of the discrepancy may be due to the anamnesis methods and the difference in the degree of disease severity, since the symptoms are associated with a milder clinical course (Yan et al. 2020) or cases without respiratory symptoms (Sinato et al. 2020). One case control study reported that the COVID-19 patients with new onset of smell and taste dysfunction were higher in number compared to influenza patients (Beltrán-Corbellini et al. 2020) and younger than those without smell and taste dysfunction (Beltrán-Corbellini et al. 2020). An objective study with 60 patients with COVID-19 using a smell-identification (40 odorants)test revealed that 98% of the patients had abnormal smell function. Among them, 58% were anosmic or severely microsmic (Moein et al. 2020). The number of reported participants of those studies is still very small compared to the actual number of COVID-19 cases. More details and comprehensive data will give a clearer assessment. Nonetheless, anosmia and ageusia have been included as symptoms and risk factors associated with COVID-19 based on the latest guidance of clinical management of COVID-19 (WHO 2020a).

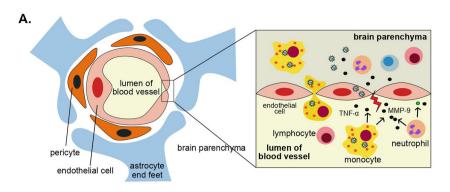
Other symptoms related to peripheral nervous system involvement are symptoms of muscle injury such as fatigue and limb aches (Mao et al. 2020) as well as pain and muscle soreness (Yin et al. 2020). Reports of CNS involvement include dizziness and headache (Mao et al. 2020), impaired consciousness (Mao et al. 2020; Moriguchi et al. 2020; Tapé et al. 2020; Yin et al. 2020), seizures (Lu et al. 2020; Moriguchi et al. 2020), psychiatric symptoms (Yin et al. 2020), diffuse corticospinal tract signs (Helms et al. 2020), ataxia (Mao et al. 2020) and acute cerebrovascular events, including ischemic stroke and cerebral hemorrhage (Mao et al. 2020). Though stroke is not uncommon among patient with COVID-19, it remains undetermined whether COVID-19 directly causes stroke. Recent reports suggested that history of stroke increased the risk of severe COVID-19 cases (Aggarwal et al. 2020a). Some of the patients have positive polymerase chain reaction (PCR) results from nasal swab samples (Yin et al. 2020) but others get negative nasal swab results while the virus was detected in the cerebrospinal fluid (CSF) (Moriguchi et al. 2020). Respiratory symptoms may occur in some cases while others may have normal chest X-rays (Tapé et al. 2020).

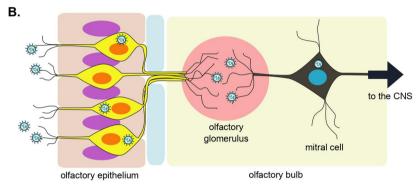
The possible route of infection into the brain

The presence of 80-110 nm viral particles with beta coronavirus characteristics has been observed in the transmission electron microscopy samples from frontal lobes of patients with COVID-19 (Paniz-Mondolfi et al. 2020). Similarly, related coronavirus particles have been detected in neurons of the victims of previous viral outbreaks (Ding et al. 2004; Gu et al. 2005). The expression of ACE2 in neurons and endothelial cells (Hamming et al. 2004) as well as in astrocytes (Gowrisankar et al. 2016) suggests that SARS-CoV-2 may have a high neuroinvasive potential. Indeed, human brain organoid studies (Mesci et al. 2020: Ramani et al. 2020; Song et al. 2020) and in vivo study in mice overexpressing human ACE2 showed that SARS-CoV-2 able to infect neuron (Song et al. 2020; Sun et al. 2020). However, mixed result of SARS-CoV-2 RNA detection in brain and CSF was reported (Moriguchi et al. 2020; Schaller et al. 2020; Solomon et al. 2020). Coronavirus infection into monocytes has been reported (Desforges et al. 2007). Indeed, single-cell RNA-seq also detected viral RNA in macrophages in bronchoalveolar lavage fluid of COVID-19 patients, though it is uncertain whether the macrophage is infected or phagocytose virus-infected cell (Bost et al. 2020). However, infected monocytes in blood circulation may bring the virus to other organs, including nervous tissue (Figure 1A). Endothelium may be infected as well and become the entry point into the brain parenchyma, as observed in monkeys infected with coronavirus (Cabirac et al. 1993). Expressions of ACE2 as well as CD147, another SARS-CoV-2 receptor (Wang et al. 2020), by endothelial cells (Jin et al. 2017) enable viral spread via blood circulation into many organs. Invasion by coronaviruses into the brain correlates with virus-induced disruption of tight junctions on brain microvascular endothelial cells, leading to blood brain barrier (BBB) dysfunction and its enhanced permeability. One recent report showing viral particles coming from capillary walls in brain samples of patients with COVID-19 support the pathogen entry through brain microvascular into brain parenchyma (Paniz-Mondolfi et al. 2020). Post-mortem brain MRI scan of COVID-19 patients also showed brain parenchymal abnormalities which suggested blood brain barrier breakdown (Coolen et al. 2020). However, mixed autopsy result of patients with COVID-19 was found. Several autopsies showed microglial activation and T cell infiltration in brain parenchyma (Hanley et al. 2020; Schurink et al. 2020) but other autopsies demonstrated lack of immune cell infiltration and cerebrovascular inflammation (Kantonen et al. 2020; Schaller et al. 2020; Solomon et al. 2020).

Many COVID-19 cases reported ageusia and/or anosmia without any clinically significant nasal congestion or rhinorrhea. This observation supports the suggestion that SARS-CoV-2 is a neurotropic virus that may invade the olfactory system (Figure 1B) (Xydakis et al. 2020). The invasion of coronavirus via olfactory mucosa into the brain was shown in transgenic mice expressing human ACE2 that were infected with SARS-CoV (Netland et al. 2008) and in monkeys exposed to coronavirus via intranasal inoculation (Cabirac et al. 1993). A dataset of single-cell RNA-seq of olfactory epithelium in mice and humans showed that ACE2 and TMPRSS2 are expressed by sustentacular cells, Bowman's gland cells and basal cells in the olfactory epithelium, but not by olfactory sensory neurons (Brann et al. 2020). However, olfactory sensory neurons express CD147 (Wang et al. 2020) and neuropilin-1 (NRP1) (Canturi-Castelvetri et al. 2020) which can mediate viral entry. Moreover, autopsy of patients with COVID-19 showed SARS-CoV-2 infected NRP1-positive cells in olfactory epithelium, as well as in olfactory tract and bulb (Canturi-Castelvetri et al. 2020). Study in mice also demonstrated that NRP1 can mediate the transport of virus-sized particle from intranasal into the brain (Canturi-Castelvetri et al. 2020). Furthermore, postmortem brain MRI scan and autopsy of patients with COVID-19 also discovered asymmetric olfactory bulb (Coolen et al. 2020), and microglia activation, astrogliosis, as well as T cells infiltration in the olfactory bulb (Schurink et al. 2020), further indicating that olfactory neuroepithelium may be mediating viral entry.

Another potential entry route into the brain parenchyma exists in the form of passage between the meninges and ventricular wall employed by coronaviruses that reach the blood vessels in meninges. The passage reported in mice models was found to be constructed between the fourth ventricle and meninges at the cerebellopontine angle upon virus infection. The construct of the fibers mimics the reticular fibers of the fibroblastic reticular network, which comprises a conduit system in the lymphoid organs (Watanabe et al. 2016). Loss of Cx43mediated functional gap junction in meningeal fibroblasts following coronavirus infection in mice might also affect BBB permeability (Bose et al. 2018) which leads to rapid viral dissemination and enhanced influx of immune cells into the brain.





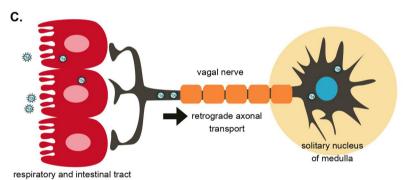


Figure 1: Possible coronavirus routes of infection into the brain. (A) Infected monocytes in blood circulation bring the virus to the brain which is followed by virus-induced disruption of tight junctions on the brain's microvascular endothelial cells which leads to BBB dysfunction (Paniz-Mondolfi et al. 2020). (B) Neuroinvasion of coronavirus via olfactory epithelium. (C) Retrograde axonal transport by which coronavirus spreads from respiratory and/or intestinal tract into the brain via the vagal nerve.

Retrograde transport machinery can be utilized for viral transfer along the axon into perikaryon (Figure 1C) (Li et al. 2013; Shindler et al. 2011). Disruption of microtubules with colchicine and vinblastine significantly blocks neuronal transport and reduces the replication of murine hepatitis virus (MHV) (Biswas and Das Sarma 2014). Viral spreading from the respiratory tract into the brain via vagal nerve has been shown in animal models of several respiratory viruses such as H5N1 (Matsuda et al. 2004). Perikaryon of vagal sensory neurons can be found in solitary nucleus of medulla, which is connected to respiratory center in the medulla and pons. Once the virus reaches the solitary nucleus, the respiratory center may be at danger and that may contribute to respiratory failure. Beside retrograde transport, similar to the other coronavirus,

SARS-CoV-2 may also exploit the axonal endoplasmic reticulum of infected neuron to disseminate to the brain (Fenrich et al. 2020). However, recent autopsy report and post-mortem brain MRI scan of patients with COVID-19 demonstrated mixed result. One autopsy showed massive microglial activation and T-cell infiltration in medulla oblongata (Schurink et al. 2020) but other reports did not corroborate that notion as it failed to demonstrate the existence of SARS-CoV-2 and any abnormalities in the respiratory center (Coolen et al. 2020; Kantonen et al. 2020).

Possibility that the virus is transported from gastrointestinal tract into the brain should also be considered (Papatsiros et al. 2019) as it is lined by ACE2-expressing cells, has numerous neurons and is widely innervated by vagal nerve. The RNA of SARS-CoV-2 has been detected in

rectal swabs (Tang et al. 2020), and fecal samples (Wu et al. 2020a), and remains detectable for a longer time, even after negative results of PCR from nasopharyngeal swab tests.

Astrocytes are reported as the main target during the acute phase of coronavirus infection in monkeys (Murray et al. 1997). Healthy cells may be infected by the virus that comes from neighboring lytic cells. The viral infection may spread further into interconnected brain regions via axonal transport (Dubé et al. 2018; Phillips and Weiss 2011). Ultrastructural observation revealed the possibility of coronavirus trans-synaptic spreading via membrane-coated exocytosis followed by endocytosis into postsynaptic neurons (Li et al. 2013).

Immune responses against coronavirus infection in CNS

Innate immune responses

Almost all resident cells of the CNS are capable of participating in innate immunity in some capacity. The upregulated genes in response to porcine hemagglutinating encephalomyelitis virus (PHEV) infection in the mice cerebral cortex were mainly involved in immune responses, including pathogen recognition, antigen processing, cytokine signaling pathways and apoptosis-related proteases (Lan et al. 2014). During coronavirus infection, the brain's microvascular endothelial cells produce type I interferon (IFN) which may prevent disruption of tight junction and brain viral invasion (Bleau et al. 2015). Microglia activation has been demonstrated in the brain of patients with COVID-19 (Hanley et al. 2020; Schurink et al. 2020). Microglia recognizes coronavirus and produce type I IFN as well (Roth-Cross et al. 2008). In a mice model, low MHC class II expression caused by depletion of microglia contributed to ineffective T-cell activation and elevated virus replication, resulting in mortality (Wheeler et al. 2018). Optimal activation of microglia and their robust type I IFN response require prostaglandin D2/D-prostanoid receptor 1 (PG2/DP1) signaling (Vijay et al. 2017).

Astrogliosis was found in the brain parenchyma of deceased patients with COVID-19 (Schurink et al. 2020). Upon coronavirus infection, astrocytes mount a delayed but more robust response to infection than microglia, despite their lower basal mRNA levels of IFN- α/β -inducing components (Hwang and Bergmann 2018). Astrocytes also orchestrate the recruitment of CXCR3-expressing cells, including natural killer (NK) cells, T cells, and plasma cells by their strong capacity to produce CXCL10 (Phares et al.

2013). Upon SARS-CoV and human coronavirus (HCoV)-OC43 infection, astrocytes are one of the cellular sources of interleukin (IL)-6 (Edwards et al. 2000; Netland et al. 2008), tumor necrosis factor (TNF)-α, IL-1b, and inducible nitric oxide synthase (iNOS) (Edwards et al. 2000; McCray et al. 2007).

Different from astrocytes and microglia, neurons carry very few MHC class I protein but they can release proinflammatory cytokines including IL-6 upon coronavirus infection (Netland et al. 2008). Oligodendrocytes poorly express type I IFN and their pattern recognition receptors (PRRs) expression is delayed and not as robust as microglia, thus they need signals from other cells to generate an antiviral state (Kapil et al. 2012). Another component of the nervous system, the satellite cells are able to restrain PHEV dissemination by engulfing the virion released from infected neurons. The virus particles are contained within vesicles and lysosome-like structures inside the satellite cells' cytoplasm (Li et al. 2012).

Following MHV infection in the CNS, CCL3, CCL5, CXCL10 (IFN-y-induced protein 10/IP10), and CXCL9 (monokine-induced by IFN-y/MIG) regulate immune cells recruitment into the brain. Accumulation of macrophages, CD8⁺ T cells and NK cells in the brain reduced viral load and increased survival (Glass et al. 2004; Trifilo et al. 2003; Trifilo et al. 2004). CXCR2-expressing cells including polymorphonuclear cells aid in host defenses through increasing the permeability of the BBB. During chronic disease, CXCR2 signaling on oligodendrocytes protects these cells from apoptosis and restricts the severity of demyelination (Marro et al. 2012). CXCL1 expression within the CNS after coronavirus infection correlated with reduced mature oligodendrocytes and increased demvelination severity caused by increased neutrophil infiltration (Marro et al. 2016). A patient with COVID-19 with demyelinating lesions that recovered upon anti-inflammatory treatment with corticosteroid has been reported (Zanin et al. 2020).

Influx of inflammatory cells is associated with matrix metalloproteinase (MMP) expression. MHV infection induces expression of MMP-3 in astrocytes and MMP-12 in CNS resident cells and infiltrating cells (Zhou et al. 2005). MMP-9 secreted by infiltrating neutrophils, macrophages, and NK cells contributes to the loss of BBB integrity by degrading claudin 5 and ZO-1 (Zhou et al. 2009), thus mediating subsequent influx of inflammatory cells into the CNS (Zhou et al. 2003). Monocytes are among the first cells along with neutrophils and NK cells that enter the brain parenchyma (Templeton et al. 2008). Neutrophils' role in viral infection of CNS was reviewed recently (Grist et al. 2018). Neutrophil infiltration promotes control of viral

replication by increasing BBB permeabilization, thus allowing specific lymphocytes access to the infected tissue (Grist et al. 2018).

Adaptive immune responses

Besides triggering local and peripheral innate immune responses, SARS-CoV-2 infection also recruits adaptive immune responses (Table 1). Perivascular and parenchymal infiltrates of T cells have been detected in the brain of patients with COVID-19 (Bryce et al. 2020; Hanley et al. 2020; Schurink et al. 2020; von Weyhern et al. 2020). CD8⁺ T cells are essential to control viral clearance from resident glia by secreting IFN-y, granzyme B, and perforin. Perforinmediated cytolysis eliminates MHV from astrocytes and microglia (Bergmann et al. 2004) and IFN-y regulates MHV replication in oligodendrocytes (González et al. 2006). Cytolytic activity of CD8⁺ T cells and their migration to the CNS are enhanced by mir-155, where its ablation increases the morbidity and mortality associated with increased viral titer (Dickey et al. 2016). Natural killer group 2 member D (NKG2D) signaling in the CNS also augments CD8⁺ T cells cytotoxic activity (Walsh et al. 2008). After crossing the BBB, CD4⁺ T cells accumulate around blood vessels. In contrast, CD8⁺ T cells enter the parenchyma. This trafficking difference is due to the expression of tissue inhibitor of MMPs (TIMP-1) by CD4⁺ T cells but not CD8⁺ T cells (Zhou et al. 2005). CD4⁺ T cells secrete IFN-y, facilitating viral clearance from oligodendrocytes (González et al. 2006), upregulating MHC class II on microglia (Bergmann et al. 2003) and MHC class I expression in oligodendrocytes (Malone et al. 2008), thereby enhancing immune cell activity in CNS. Inhibition of death-associated protein kinase (DAPK)-related apoptosis-inducing kinase 2 (DRAK2) signaling following MHV infection amplified antiviral response of memory T cells and elevated IFN-y levels which were correlated with reduction of viral load in infected mice (Schaumburg et al. 2007).

Accumulation of Ab-secreting cells (ASC) in the CNS following MHV infection occurs after their maturation in peripheral lymph nodes and is CXCR3/CXCL10-dependent (Phares et al. 2013). Virus-specific IgM was initially detected at day 7 postinfection (p.i.) and antiviral IgG was initially detected at day 10 p.i (Tschen et al. 2002). Following elimination of infectious virus, CXCL13 secreted by microglia promotes accumulation of isotype-switched B cells (Phares et al. 2016) within the CNS and these cells remain stable during virus persistence, in contrast to the declining T-cell numbers, suggesting their role in controlling virus recrudescence.

Table 1: Immune responses against coronavirus infection in the central nervous system.

Cells	Action
Microglia	Main antigen presenting cells in the brain; recognizes viral antigen via PRR; produces type I IFN; expresses MHC class I and II; pro- duces CXCL13 to induce B cells isotype switch
Astrocytes	Produce type I IFN, IL-6, TNF- α , IL-1b, iNOS; express MMP3; secrete CXCL10 which act as recruitment signal of T cells, B cells, and NK cells into the brain
Neuron	Produces IL-6; but has low expression of MHC class I
Oligodendrocytes	Low expression of PRRs and type I IFN; express MMP12; need stimulation from other cells to mount antiviral activity
Brain microvascular	Produce type I IFN to maintain BBB integrity
endothelial cells (BMEC)	and prevent viral invasion into the brain
Satellite cells	Engulf and destroy virus particles via endoly- sosomal pathway
Neutrophils	Release MMP9 that leads to the increase of BBB permeabilization and facilitate the infiltration of virus-specific T cells into the brain
Macrophages	Produce MMP9; secrete type I IFN, thus limiting viral replication
NK cells	Secrete MMP9 and IFN-γ
CD8 ⁺ T cells	Produce IFN-γ; destroy virus-infected cells through its cytolytic activity
CD4 ⁺ T cells	Produce IFN-y; upregulate MHC class II expression in microglia and MHC class I in oligodendrocytes; increase CD8 ⁺ T cells survival in brain parenchyma
Regulatory T cells	Inhibit T cells activation and migration form
(Treg)	peripheral lymph node, thus decrease T cells number in the brain; decrease activation of microglia; produce IL-10
Plasma cells	Produce IgM and IgG; their number are stable during virus persistence period, thus controlling virus recrudescence

BBB, blood brain barrier; IFN, interferon; Ig, immunoglobulin; IL, interleukin; iNOS, inducible nitric oxide synthase; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NK, natural killer; PRR, pattern recognition receptor; TNF-α, tumor necrosis factor-α; Treg, regulatory T cells.

Virus-specific Tregs repress the activation of effector T cells from naïve T cells (Zhao et al. 2014). Tregs inhibit the migration of CD4⁺ T cells from the draining lymph nodes. In addition, Tregs diminish microglia activation and decrease the number and function of effector T cells in the infected brain (Zhao et al. 2014). Depletion of Tregs in mice infected with MHV increased mortality while adoptive transfer of Tregs increased survival (Anghelina et al. 2009). Tregs secrete IL-10 that has been shown to prevent encephalomyelitis and demyelination in rat models of coronavirus infection (Trandem et al. 2011). In mice infected with MHV, the balance of antiviral state of type I IFN and antiinflammatory IL-10 prevents tissue damage while not compromising elimination of the virus. The role of immune regulation in viral infections of the brain has been reviewed recently (Savarin and Bergmann 2018).

Detection of SARS-CoV-2 RNA in the nasopharynx has been reported in patients that previously had negative results. Several issues including the sensitivity of the tests, reinfection due to inadequate neutralizing antibodies in mucosa and viral hiding in immune cells has been suggested to explain the phenomenon. Additionally, suggestions have been discussed that coronavirus may have a latency period in neurons or astrocytes (Arbour and Talbot 1998). However, whether SARS-CoV-2 does hide inside neuronal cells, and may be released in certain conditions remains unclear.

Mechanism of nerve degeneration upon coronavirus infection

Viral infection of the nervous system can be damaging. Brain samples of a patient with COVID-19 showed distended viral particle-containing cytoplasmic vacuoles in neuronal cell bodies (Paniz-Mondolfi et al. 2020) proving viral

propagation inside neuron. Several possible mechanisms of neuronal degeneration upon coronavirus infection have been described in a recent review (Wu et al. 2020b). Here we discuss them with a slightly different approach while adding some more recent findings (Figure 2).

During SARS-CoV-2 infection, respiratory distress may occur due to lung inflammation and blood clotting, hence the oxygen distribution into many organs is inadequate. Anemia is also reported in patients with SARS-CoV-2 due to hemoglobin dysfunction (Henry et al. 2020). In severe cases, systemic inflammation contributes to inadequate circulation. As the body's organ with the largest oxygen demands, the brain's hypoxia immediately leads to neuronal adenosine triphosphate (ATP) crisis making cells prone to necrosis (Tanaka et al. 2005). Intermittent hypoxia may upregulate the expression of glial inflammatory gene expression (Hocker et al. 2017). The high level of inflammatory cytokines not only enhances the inflammatory state in the organ but also coagulopathy and thrombosis (Merad and Martin 2020), which may block blood vessels and lead to cerebrovascular accidents (Hess et al. 2020). The role of SARS-CoV-2 receptors, i.e., CD147 in inducing inflammation and thromboembolism may contribute to ischemic stroke, as has been shown in animal models of cerebral arterial occlusion (Jin et al. 2017).

Upon viral infection, neurons may die via several mechanisms such as cell lysis, oxidative stress, and

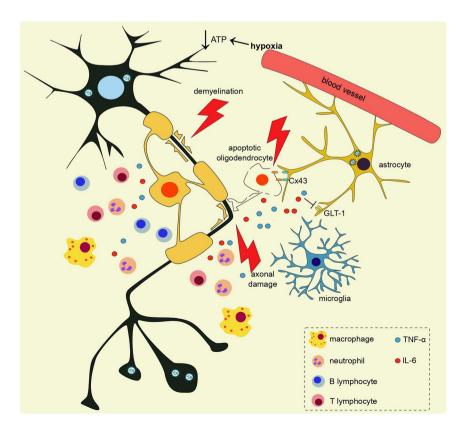


Figure 2: The mechanism of neurodegeneration upon coronavirus infection may involve several pathways. Brain hypoxia due to inadequate circulation induced by systemic inflammation or cerebrovascular accident leads to neuronal ATP crisis that may lead to necrosis. BBB disruption may lead to peripheral immune cells infiltration into the brain. Together with microglia, these infiltrating immune cells release proinflammatory cytokines, including TNF-α and IL-6 that cause glutamate excitotoxicity and mediate axonal damage. Neutrophils and microglia accumulation, as well as downregulation of Cx43 in neurons and glia also contribute to apoptotic oligodendrocytes and demyelination.

mitochondrial dysfunction (Song et al. 2013). Lack of proper growth factor signaling may induce apoptosis such as shown by infection of PHEV that inhibits normal function of Unc51-like kinase (Ulk1) in the retrograde transport of nerve growth factor/TrkA-containing endosomes (Li et al. 2018). Downregulation of genes that are mainly involved in synaptic transmission, neuron-projection development and the transmission of nerve impulses (Lan et al. 2014), compromises the neuronal function. Direct insult by coronavirus toward neurons may involve the increased production of viral proteins and viral particles which elevate endoplasmic reticulum (ER) stress and cause greater activation of unfolded protein response (UPR) (Song et al. 2013) that eventually triggers necroptosis (Meessen-Pinard et al. 2017).

The indirect insult can be mediated by immune cells including microglia and macrophages (Kakizaki et al. 2014). Immune responses elicited by CD4⁺ and CD8⁺ T cells also mediate axonal damage after coronavirus infection (Dandekar et al. 2001). Activated immune cells, primarily microglia, and the released proinflammatory cytokines, including TNF-α and IL-6 may downregulate the glutamate transporter GLT-1 on astrocytes, thereby disrupting glutamate reuptake and causing glutamate excitotoxicity (Brison et al. 2011). Upon coronavirus infection, groups of neurons connected in the same circuit may die concomitantly or one after another creating the appearance of spongiform degeneration (Kashiwazaki et al. 2011) as described in prion diseases.

Apoptotic oligodendrocytes upon coronavirus infection have been detected (Liu et al. 2006) especially in the areas with demyelinating lesions (Schwartz et al. 2002). Demyelination after MHV infection may occur via downregulation of Cx43 in neurons and glia (Basu et al. 2015), as the functional gap junction formed by Cx43 coupled with oligodendrocytic Cx47 is important in maintaining oligodendrocytes function and myelin formation (May et al. 2013). The reduced number of oligodendrocytes and demyelination may correlate with neutrophil infiltration during brain inflammation as has been shown in mice models of viral infection (Marro et al. 2016). Neutrophilmediated neuropathology and its correlation with demyelination were reviewed recently (Grist et al. 2018). Microglial accumulation is observed in demyelinating plaque and clearly associated with the pathology of MHV-induced demyelination. Appearance of CD11cexpressing macrophages from blood that exhibit properties of immature APCs, are closely associated with areas of demyelination, and may act as final effectors of myelin destruction (Templeton et al. 2008).

Associated neurological damage and neuroplasticity: long-term consequences for the survivors?

Past pandemics have showed that various neurological diseases may follow acute viral infection by weeks, months or even longer in survived patients (Lee et al. 2007; Tan et al. 2010). Neurological complications including limb weakness, hyporeflexia, paresthesia, and hypesthesia have been described 3-4 weeks following SARS-CoV and MERS-CoV infection (Kim et al. 2017; Tsai et al. 2004). Indeed, mice surviving from acute encephalitis caused by HCoV infection exhibited decreased locomotor activity, smaller hippocampus and neuronal loss in CA1 and CA3 layers which may induce deficits in learning and memory (Jacomy et al. 2006). In a mouse model of Alzheimer disease, MHV infection-induced inflammation exacerbates tau pathological features which may lead to motor and cognitive impairments (Sv et al. 2011).

Immune responses against viral infection may trigger the development of neurological autoimmune diseases such as MS (Fierz 2017). The mechanisms, including persistence inflammation due to sustained IFN production, have been discussed recently (Crow et al. 2019). Additionally, HCoV-OC43 was detected in the brain tissues of 48% of patients with MS (Arbour et al. 2000). Moreover, selfreactive T cells from patients with MS and MHV-infected mice recognize viral and myelin antigens (Boucher et al. 2007; Gruslin et al. 2005). In MHV-infected mice, the existence of self-reactive CD4+ T cells in the CNS coincides with the demyelination process during acute infection (Savarin et al. 2015). Guillain-Barre syndrome (GBS) is another autoimmune-mediated disease with neurological damage, for which SARS-CoV-2 infection might be responsible (Scheidl et al. 2020; Zhao et al. 2020). Administration of exosomes containing viral antigens from patients with respiratory viral infection triggered autoimmune reactions in mice models (Gunasekaran et al. 2020). On the contrary, the immune regulatory system involving antigen-specific IL-10 secreting CD4⁺ T cells (Tr1) activated during viral persistence, may prevent autoimmune disease via inactivation of self-reactive CD4⁺ T cells in the CNS (Savarin et al. 2016). More studies on immune regulation upon viral infection in correlation to prevention of virus-related autoimmune diseases should be encouraged.

Involvement of the gastrointestinal tract in SARS-CoV-2 infection opens another threat for the nervous system because it may increase the induction and transport of aberrant proteins such as α-synuclein that are related to neurodegenerative diseases (Kim et al. 2019). Inflammationinduced bacterial leakage from the gastrointestinal tract may also bring bacterial components and metabolites into the brain parenchyma leading to brain pathology (Srikantha and Mohajeri 2019). Some opinions and warnings have been recently published elsewhere (Pereira 2020).

Reports of a multicenter study in China revealed no increased risk of developing seizures in patients with COVID-19 but they also recommended prospective longterm studies to address the issue (Lu et al. 2020). Behavioral host manipulation by which a pathogen manipulates the behavior of the host to maximize its transmission has been reported in several pathogens including toxoplasmosis and influenza (Reiber et al. 2010; Vyas et al. 2007). Currently, evidence of behavioral host manipulation in patients with COVID-19 is still lacking, but it would be of special interest if SARS-CoV-2 is able to cause such behavioral changes in its host (Barton et al. 2020). Antibodies against HCoV were detected in patients with recent psychotic episodes, suggesting there is some relationship between coronavirus infection and psychosis (Severance et al. 2011). Other more serious concerns about neuropsychiatric sequelae of COVID-19 have been proposed in a recent review (Troyer et al. 2020).

How to protect and fight back?

Immunomodulatory effects of the autonomic nervous system may be beneficial in prevention of the hyperinflammatory state leading to severe manifestations of COVID-19. Keeping the immune activity in a modest yet effective response may eliminate the pathogens while limiting organ damage including CNS involvement. Mindfulness and meditation have been suggested as an essential part of COVID-19 management (Behan 2020). So far, only one study with limited patients reported the benefit of vagal nerve stimulation as part of the management of patients with COVID-19 (Staats et al. 2020).

Some neurons such as the interneurons of mice olfactory bulb can survive coronavirus infection (Wheeler et al. 2017). Studies of differential gene expression in those neurons may provide valuable data that can be translated into strategies for neuroprotection in acute neurotropic viral infection. Effective anti-inflammatory treatments should be investigated. IL-10 treatment in MHV-infected mice has been reported to induce glial scar formation by astrocytes that limit the demyelination areas (Puntambekar et al. 2015). After myelin destruction, remyelinating may occur via upregulation of genes involved in oligodendrocytes maturation such as Oncostatin M (Glezer and Rivest 2010), as has been shown in mice infected with MHV (Elliott et al. 2013). Whether the degree of remyelination has a role in the outcome of the disease remains to be investigated.

Observations of inhibitory activity of prostaglandin D2/D-prostanoid receptor 1 on virus-induced inflammasome and IL-1b secretion (Vijay et al. 2017) may provide an alternative to negatively regulating immune responses to prevent hyperinflammation. Inhibition of CD147, one of the SARS-CoV-2 receptors may have additional benefits in preservation of oligodendrocytes and white matter, which has been reported in mice models of ischemic stroke (Liu et al. 2019). However, antibodies against CD147 also permeabilize BBB by binding to CD147 in the brain endothelial cells (Zuchero et al. 2016), hence, enhancing brain inflammation with its double-sided sword effect, may be either beneficial or detrimental. Appropriate timing for COVID-19 treatment related to its varied clinical manifestations is a difficult challenge that should be overcome as soon as possible.

Traditional medicine with neurological benefits should also be explored. Traditional Chinese medicine was used during the SARS outbreak with some evidence showing its benefits for treatment and prevention of SARS (Yang et al. 2020), yet there were no reports on their neuroprotective effects. Several herbal and traditional medicines are reported to have neuroprotective effects, including curcumin (Reddy et al. 2018), Centella asiatica (Ar Rochmah et al. 2019), andrographolide (Lu et al. 2019), and astragalus polysaccharides (Liu et al. 2018). Ginkgolic acid, a component of Ginkgo biloba, hampers virus entry by blocking its fusion into susceptible cells, hence, it has potential to be used in SARS-CoV-2 infection (Borenstein et al. 2020).

Development of a vaccine for SARS-CoV-2 is one of the top priority strategies to overcome COVID-19. Because SARS-CoV-2 primarily infects mucosa of the lungs, the vaccination strategy should induce specific immune responses in the lungs. Intranasal administration is known for its excellent induction of immune responses in mucosa of respiratory tract (See et al. 2006). However, considering the possibility of SARS-CoV-2 entering the CNS through olfactory epithelium and reports of neurological sideeffects following intranasal vaccination (Lemiale et al. 2003), sublingual administration should be preferred instead of the intranasal route (Shim et al. 2012).

Translational neuroscience is necessary to elucidate CNS involvement in coronavirus infection. Indeed, lessons learned from animal models used in the study of SARS and MERS are valuable to understand the viral pathogenesis and dissemination in the CNS (Gretebeck and Subbarao 2015; McCray et al. 2007; Netland et al. 2008). So far, with

animal models, researchers were able to confirm neuronal vulnerabilities for coronavirus infection (Netland et al. 2008), investigate the potential route of CNS entry (Brann et al. 2020; Cabirac et al. 1993; Netland et al. 2008), and the pathogenesis of SARS-CoV-2 infection (Bao et al. 2020). However, the multiple human specific receptors used by SARS-CoV-2 invasion, i.e., ACE2 and CD147 (Wang et al. 2020), as well as the differences of the host characteristics that influence the responses to the viral infection (Conti and Younes 2020; Nikolich-Zugich et al. 2020; Rouse and Sehrawat 2010) complicate these efforts.

Last but not least, raising the awareness of the damaging effect of SARS-CoV-2 infection and also on the importance of early neurological management of patients with COVID-19 should be encouraged. Clinical examinations including a variety of reflex examinations and CSF detection of viral particles for early management of neurological complications should be considered to minimize any potential neurological damage (Li et al. 2020b).

Limitation

Though report on neurological involvement of COVID-19 is frequent, many of the mechanisms underlying the involvement are yet to be elucidated. Thus, in addition of data from current outbreak and current research progress, this review also summarized the data from previous coronavirus outbreak and past animal studies to support the proposed hypothesis of SARS-CoV-2 neuroinvasion mechanism and neuroimmune crosstalk underlying the neurological involvement of COVID-19. Due to the rapid pace of research progress in the field of COVID-19, this review may not be able to cover all data from the latest research progress. Moreover, some of the articles cited in this review are yet to be peer-reviewed. Despite these limitations, this review strives to provide the latest data and current knowledge on this topic.

Conclusions

Evidence of neurological symptoms of SARS-CoV-2 infection is indisputable and should be investigated and considered during COVID-19 management. However, studies of the many aspects concerning nervous tissues' substantial involvement in the current pandemic are still in the beginning point of elucidation and far from definitively clear. Previous coronavirus outbreaks and studies on animal models may give some clues of the pathogenesis and possible therapeutic modalities that should be tested for efficacy in COVID-19 cases. The importance of the complex interactions between the nervous and immune systems upon SARS-CoV-2 infection should be elucidated to minimize its possible long-lasting and damaging neurological manifestations.

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