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REVIEW

COVID-19 virus may have neuroinvasive potential and cause neurological complications: a perspective review

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Abstract

Coronavirus disease 2019 (COVID-19) was reported at the end of 2019 in China for the first time and has rapidly spread throughout the world as a pandemic. Since COVID-19 causes mild to severe acute respiratory syndrome, most studies in this field have only focused on different aspects of pathogenesis in the respiratory system. However, evidence suggests that COVID-19 may affect the central nervous system (CNS). Given the outbreak of COVID-19, it seems necessary to perform investigations on the possible neurological complications in patients who suffered from COVID-19. Here, we reviewed the evidence of the neuroinvasive potential of coronaviruses and discussed the possible pathogenic processes in CNS infection by COVID-19 to provide a precise insight for future studies.

Keywords Coronavirus · Neuroinvasion · Nervous system · COVID-19 · Transmission routes

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
BBB	Blood-brain barrier
CNS	Central nervous system
CoV	Coronavirus
CoVs	Coronaviruses
COVID-19	Coronavirus disease 2019
HCoVs	Human coronaviruses
HCoV-OC43	Human coronavirus OC43
HCoV-229E	Human coronavirus 229E
MERS	Middle East respiratory syndrome
SARS	Severe acute respiratory syndrome

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Introduction

Coronaviruses (CoVs) belong to a large family of viruses that cause diseases in mammals and birds (Liu et al. 2020). CoVs are responsible for severe respiratory illness such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) in humans. Six types of these viruses affect human cases, such as 229E, NL63, OC43, HKU1, MERS-CoV, and SARS-CoV (Matoba et al. 2015; Myint 1995). A novel CoV (SARS-CoV-2) also known as COVID-19 has been reported in China in December 2019 for the first time (Lam et al. 2020). Recently, the World Health Organization (WHO) has declared that new coronavirus disease is a pandemic. The symptoms of COVID-19 are very similar to MERS and SARS including shortness of breath, breathing difficulties, cough, fatigue, sore throat, and fever. Likewise, some symptoms such as headaches, nausea, confusion, dizziness, and vomiting are reported (Jiang et al. 2020). Studies have shown that MERS-CoV, SARS-CoV, and COVID-19 may cause acute respiratory distress syndrome (ARDS), hepatic, and intestinal diseases (Leung et al. 2003; Peiris et al. 2003; Wu et al. 2020; Zhang et al. 2020). It has been indicated that 229E-CoV, OC43-CoV, and SARS-CoV lead to neurological complications in some patients and

animal models (Bonavia et al. 1997; Desforges et al. 2014; Jacomy et al. 2006; Jevšnik et al. 2016; Li et al. 2016b; St-Jean et al. 2004) (Table 1). Since the structure and pathogenesis of most CoVs are similar (Butler et al. 2006; St-Jean et al. 2004; Yuan et al. 2017) and the behavior of COVID-19 is unknown, attention to the other organs which may be involved (e.g., central nervous system) and follow-up of patients for neurological complication by designing perspective cohort studies are essential. Therefore, the aim of the present study was to review neuroinvasive potential and neurotropism effects of human coronaviruses (HCoVs) and discuss the probable neurological complication followed by COVID-19 to give an insight for future studies.

Search strategy and selection criteria

References for this review were classified through searches of PubMed and Google Scholar for articles published from 1967 to April 15, 2020. We used the terms "coronavirus," "SARS," "SARS-CoV-2," "MERS," "229E-CoV," and "COVID-19," with combination the terms "nervous system," "neuroinvasion," and "neurological manifestation." In vitro studies on neurotropism potentials of CoVs on neural or glial cells cultures were considered. Furthermore, in vivo investigations were included for injection routes (intranasal and intraperitoneally) of neuroinvasion. Finally, clinical finding searched and included for neurological signs related to CoVs infections.

How can CoVs enter the CNS?

Data from clinical and animal studies have shown that CoVs can cross the blood-brain barrier (BBB) and exert neuroinvasive properties (Cabirac et al. 1994; Cavanagh 2005; Desforges et al. 2013; Li et al. 2016b; Niu et al. 2020; Talbot et al. 2011; J. Xu et al. 2005). The precise mechanisms of penetration into the CNS have not been fully understood. However, four routes of transmission have been suggested. First of all, olfactory nerves are an accessible route for the invasion of CoVs into the CNS (Fig.1 (1)). Intranasal inoculation of mice with MERS-CoV causes brain infection with the involvement of thalamus and brain stem (Li et al. 2016a). Furthermore, it has been reported that the rate of mortality in mice was increased when infected with SARS-CoV through intranasal inoculation. It might be due to neuroinvasion and neural death in the brain stem (Netland et al. 2008). Cellular invasion is the second way to enter the CNS (Fig. 1 (2)). In this way, infected monocytes/macrophages by CoVs cross the BBB and exert neuroinvasive properties. MERS-CoV can infect monocyte and T lymphocyte in human cell lines (Chan et al. 2013). In vitro studies have reported that infected human monocytes/macrophages can act as a viral reservoir and spread viruses to other tissues (Collins 2002; Desforges et al. 2007). The third possible way which mediates neuroinvasion of CoVs is microvascular endothelial cells of BBB structure (Fig.1 (3)). These cells can express two types of SARS-CoV receptors, such as angiotensin-converting enzyme 2 (ACE2) and CD209L (J. Li et al. 2007). Therefore, SARS-CoVs can enter the CNS through interaction with ACE2 and CD209L receptors. The last transmitting way into the CNS is trans-synaptic transmission through peripheral nerves (Figs.1 (4)). Injection of hemagglutinating encephalomyelitis virus (HEV) in hindfoot of rat leads to the emersion of the virus in the motor cortex through coated vesicles in trans-synaptic route (Li et al. 2013).

Human coronavirus family has neuroinvasion potential

Evidence suggests that several types of infected human coronavirus have neuroinvasion potential. For example, the type of human coronavirus 229E (HCoV-229E) causes neurological manifestation through neuroinvasion. Several studies have been indicated that human neural cell culture was infected by HCoV-229E (Arbour et al. 1999; Bonavia et al. 1997;

Table 1 Neurological manifestations and pathological findings related to human coronaviruses family infections

Human coronaviruses	Type of Study	Clinical signs/pathological findings	References
CoV-229E	Postmortem analysis of brain samples	Neuroinvasion in multiple sclerosis	(Arbour et al. 2000)
CoV-OC43	Postmortem analysis of brain samples or CSF sampling	Neuroinvasion in multiple sclerosis, demyelination, and encephalomyelitis	(Arbour et al. 2000; Yeh et al. 2004)
SARS-CoV	Clinical human study and postmortem analysis	Generalized tonic-clonic seizure, CSF infection, glial cells hyperplasia, neural cell necrosis, neuroinflammation, brain edema	(Gu et al. 2005; Lau et al. 2004; J. Xu et al. 2005)
MERS-CoV	Clinical human studies	Ataxia, confusion, dizziness, headache	(Algahtani et al. 2016; Kim et al. 2017)
SARS-CoV-2	Clinical human studies	Headaches, nausea, confusion, dizziness, impaired consciousness, ataxia, acute cerebrovascular diseases, vomiting, epilepsy, and skeletal muscle symptoms	(Guan et al. 2020; Li et al. 2020; Mao et al. 2020a; Mao et al. 2020b)

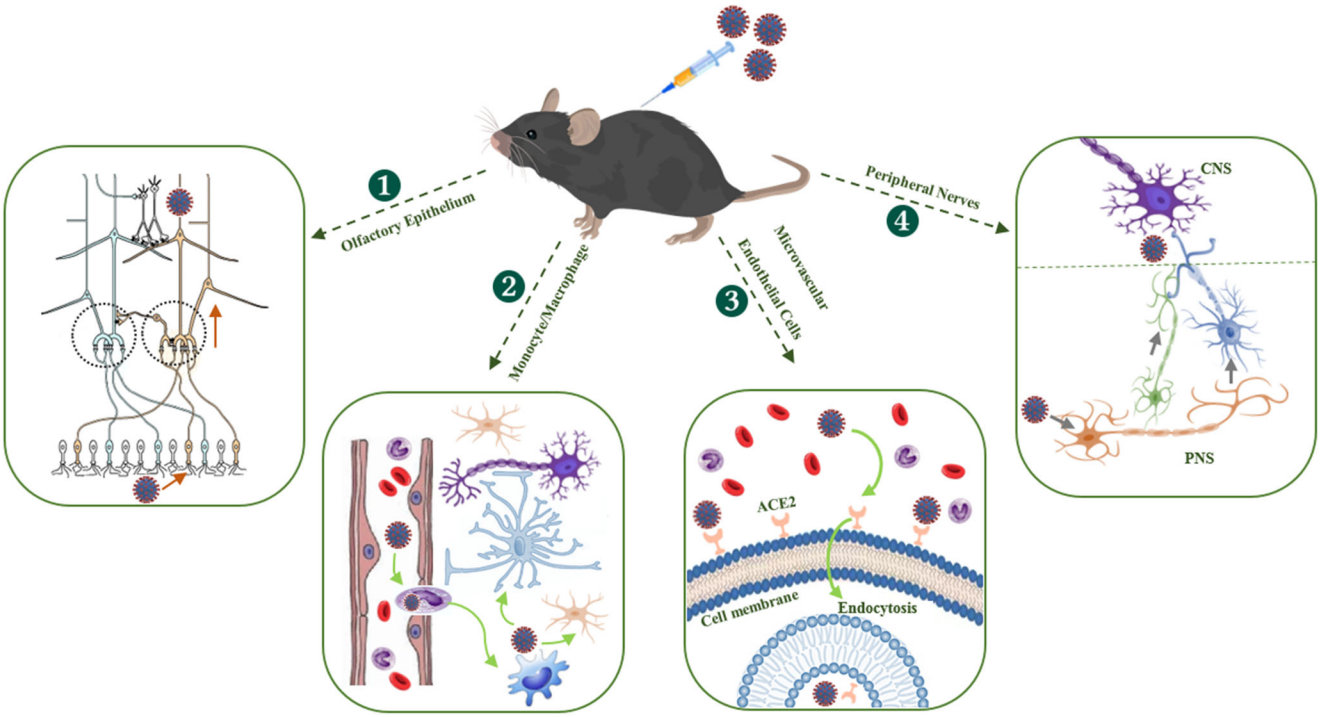

Fig. 1 Transmission routes of coronaviruses into the CNS. (1) Intranasal inoculation of coronaviruses can lead to neuroinvasion through primary olfactory neurons in the olfactory epithelium and mitral/tufted cells in the olfactory bulb. (2) Infected monocytes can cross from BBB via diapedesis and infect glial and neuronal cells. (3) Interaction between CoV and ACE2 receptors on BBB endothelial cells can enter into the CNS. (4) Finally, viruses can enter the CNS through peripheral nerves via trans-synaptic transmission. ACE2, angiotensin-converting enzyme 2; CNS, central nervous system; PNS, peripheral nervous system

Lachance et al. 1998). It has also been reported that HCoV-229E can increase the production of pro-inflammatory cytokines in monocytes (Desforges et al. 2007). Also, post-mortem analysis of brain multiple sclerosis patients showed a presence of HCoV (Arbour et al. 2000). Another human coronavirus which is very similar to HCoV-229E known as OC43 (HCoV-OC43) is responsible for the common cold and lower respiratory tract infections such as pneumonia (Vabret et al. 2003). It has been reported that neuronal cells derived from mouse dorsal root ganglia and human astrocyte cells produced HCoV-OC43 antigen and infectious virus (Pearson and Mims 1985) (Bonavia et al. 1997). The production of pro-inflammatory cytokines increased and induced neural injuries when human astrocyte culture was infected by HCoV-OC43 (Edwards et al. 2000). HCoV-OC43 (Jacomy et al. 2006; Stodola et al. 2018) caused neuropathy and gliopathy by activating the apoptosis cascades in cell cultures (Jacomy et al. 2006). Furthermore, neuroinflammation following by neuroinvasion has been shown in mice when HCoV-OC43 was inoculated intraperitoneally (Jacomy and Talbot 2003). Encephalitis, neuronal degeneration, microglia activation, and decreasing locomotor activity were also observed following the administration of HCoV-OC43 in mice (Jacomy et al. 2006). Identically, intranasal inoculation of virus leads to neuroinvasion (Butler et al. 2006; St-Jean et al. 2004). In a postmortem study, a higher prevalence of HCoV-OC43 was seen in the brain multiple sclerosis patients (Arbour et al. 2000). In a case report study, the test of HCoV-OC43 was positive in a child with encephalomyelitis (Yeh et al. 2004).

Another example of a neuroinvasive function is SARS-CoV which is identified in southern China and caused more than 900 deaths in the world until Jun 2003 (Chan-Yeung and Xu 2003) (Vu et al. 2004). SARS-CoVs could penetrate into the CNS and cause neuropathy and gliopathy (Guo et al. 2008). An increase of pro-inflammatory cytokines was observed after intranasal inoculation of SARS-CoV in mice brains. The presence of the virus in the brain tissue was confirmed by RT-PCR (McCray et al. 2007) (Netland et al. 2008). Generalized tonic-clonic convulsion has been reported in a patient who suffered from SARS disease. In this case, the presence of SARS-CoV in cerebrospinal fluid was positive (Lau et al. 2004). Also, glial cells hyperplasia and neural cell necrosis in a cytokine manner mechanism were detected in the brain sample from a patient with SARS (Xu et al. 2005). A postmortem analysis has also been shown that SARS-CoV is capable to infect the neural cells in the hypothalamus and cortex and cause brain edema in patients with SARS disease (Gu et al. 2005). Additionally, MERS-CoV as an HCoVs can infect human neuronal cell line culture (Zaki et al. 2012) (Chan et al. 2013). Also, a report study indicated that two patients with MERS-CoV infection had severe neurological

manifestations (Algahtani et al. 2016). In the same way, it has been reported that some neurological implications, such as weakness of limbs or hand and hyperreflexia in deep tendon reflex were seen in patients with MERS-CoV infection (Kim et al. 2017).

It is interesting to note that neurological signs, such as headache (Chen et al. 2020; Huang et al. 2020; Wang et al. 2020; Woelfel et al. 2020; Xu et al. 2020; Yang et al. 2020), confusion, dizziness, impaired consciousness, ataxia, epilepsy, and skeletal muscle symptoms in patients with COVID-19 were reported (Guan et al. 2020; Li et al. 2020; Liang et al. 2020; Mao et al. 2020a; Mao et al. 2020b). It might be due to neuroinvasive property. However, few researchers have been able to draw on any systematic research into this topic. But it has been recently suggested that the interaction of SARS-CoV-2 with ACE2 receptors on the neural cells can involve in the pathophysiology of neuroinvasion and neural damages following COVID-19 infection (Baig et al. 2020). Besides that, an unpublished report from Beijing Ditan Hospital showed that the encephalitis was observed in a patient with COVID-19 (Huaxia 2020). Also, neuroimaging techniques and EEG data in two new cases revealed hemorrhagic necrotizing encephalopathy (Poyiadji et al. 2020), epileptogenicity, and encephalomalacia (Filatov et al. 2020) in relation to SARS-CoV-2 infection. Furthermore, in two currently cases, a 74-year-old man and a 58-year-old woman have been confirmed with neurological manifestations as a consequence of the SARS-CoV-2 infection (Lanese 2020; Rahhal 2020). The 74-year-old patient had temporarily lost the ability to speak in Florida (Rahhal 2020). The case of 58-year-old woman had confusion, lethargy, and disorientation signs. The brain CT scans and magnetic resonance imaging (MRI) revealed injury in the thalamus, hemorrhage, and necrotizing encephalopathy (Lanese 2020). In contrast to another type of HCoVs, there is much less information about the effects of neuroinvasive and neurotropism of COVID-19.

Conclusion remarks and future perspective

Taken together, data from the above-mentioned studies confirm the neuroinvasive properties of HCoVs and their effects on CNS. Although the exact mechanism of neuroinvasion is still unclear, some penetration routes, such as olfactory epithelium, cellular infection, BBB structure, and trans-synaptic transmission, have been suggested. Considerably, more work will need to be done to determine the long-term effects of COVID-19 on CNS. Therefore, we suggest that a well-designed cohort study can provide powerful results for their effects. In the same way, further experiments using in vitro, in vivo, and postmortem studies could shed more light on the possible neuroinvasion and neural injuries after SARS-CoV-2 infection.

Authors' contributions Ali Sepehrinezhad and Sajad Sahab Negah designed the study, performed the literature review, and drafted the manuscript. Also, Ali Shahbazi and Sajad Sahab Negah critically edited the manuscript and corrected grammatical errors in the revised manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Availability of data and materials No datasets were generated during the study.

Competing interests The authors declare that they have no competing interests.

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