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SARS-CoV2 neuroinvasive potential in respiratory failure in COVID-19 patients

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the same sequence as SARS-CoV and has been reported with clinical symptoms similar to those of SARS-CoV and MERS-CoV. This study reviewed the neuro-invasive potential of SARS-CoV2 reported in various studies. We searched keywords containing COVID-19, coronavirus, respiratory infection, SARS-CoV2, and neuro-invasive potential in PubMed, WOS, Scopus, SID, and Google scholar. The results of our study led to the achievement of articles on the study of COVID-19. This study focused on published articles from 1970 to 2021. Respiratory failure was drawn as the most prominent symptom of COVID-19, while evidence suggests that SARS-CoV2 does not exclusively affect the respiratory system and may lead to neurological disease by invading the central nervous system. SARS-CoV may also cause severe brainstem infection. Some coronaviruses (CoVs) can spread through a synaptic connection to the medullary cardiorespiratory center of mechanical and chemical receptors in the lungs and lower respiratory tract. Neuro-invasive and neurotropic tendency of SARS-CoV2 has potential to cause neuropathological issues in the patients. Since there are many similarities between SARS-CoV and SARS-CoV2, recognizing the link between potential SARS-CoV2 virus attack and acute respiratory failure in COVID-19 infection is critically important in preventing and treating SARS-CoV-2 respiratory failure.

Keywords: Coronavirus, Outbreak, Acute respiratory failure, Nervous system, MERS-CoV, Neurotropic, SARS-CoV2.
Article type: Review Article.

INTRODUCTION

Coronaviruses is a positive single-stranded RNA virus (Yachou *et al*. 2020) that may cause intestinal and respiratory problems in human (Karimi *et al*. 2021). Mild respiratory disease is the major complication due to human coronaviruses including OC43, HKU1, hCoV-229E and NL63. Yet, the outbreak of two recently emerging human COVs, i.e., MERS and SARS, resulted in acute respiratory syndrome as well (Sadighara *et al*. 2022). SARS-CoV-2 was first identified in Wuhan, China in late 2019 that led to severe pneumonia in there and subsequently across China and the world (Li *et al*. 2020). Research findings have shown a similar sequence structure and pathogenesis to SARS-CoV for SARS-CoV-2, causing it to bind to the same receptors in the body

(Yu *et al*. 2020). Most CoVs share a common infection structure and pathway, and consequently SARS-CoV-2 has a mechanism of pathogenesis highly similar to the other CoVs. Human coronavirus could infect the central nervous system (CNS) causing nerve damage leading to acute respiratory distress (Li *et al*. 2020). One study on viral infection of the CNS reported that virtually all viruses could target the CNS under suitable circumstances, e.g., mutations in specific virulence genes and immunodeficiency (Koyuncu *et al*. 2013). Viral respiratory diseases are critically important from public health perspective because of considerable mortality rates. Cytokine storm due to CNS immune response to viral infection that results in various types of neurological disorders including encephalitis, meningitis, and meningoencephalitis and even death, has also been found in previous studies. This virus affects the respiratory system with neuro-invasive capabilities that cause COVID-19 infection in human with certain presentations including CNS-related complications, respiratory failure and pneumonia (Yachou *et al*. 2020).

MATERIALS AND METHODS

Search methodology

The databases including Scientific Information Databases (SID), PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect were thoroughly searched for relevant articles published from 2010 to 2020 using search terms such as coronavirus, COVID-19, respiratory infection, SARS-CoV2, and neuro-invasive potential in their titles.

RESULTS AND DISCUSSION

SARS-CoV-2 infection clinical manifestation

This virus causes acute and deadly pneumonia and has clinical manifestation similar to MERS and SARS (Li *et al*. 2016). As Table 1 shows, the imaging observations of majority of SARS-CoV infection patients with fever, shortness and dry cough contained bilateral ground-glass opacification/opacity (GGO) on chest CT scan (Dubé *et al*. 2018). In contrast, SARS-CoV-2 infection patients rarely had remarkable symptoms involving their upper respiratory tracts, which reveals that SARS-CoV-2 target cells may exist in the lower airways (Sadighara *et al*. 2022). The first symptoms of COVID-19 infection are fever and dry cough. The most common symptom in these patients is respiratory distress (about 55%) and half of the patients with shortness of breath require intensive care services. The conditions in 46-65% of ICU patients exacerbate shortly after admission and eventually decease due to respiratory failure. Approximately 89% of COVID-19 infection cases require critical care for breathing (Li *et al*. 2016). Recent evidence has also indicated that coronaviruses can lead to neurological disorders. This neuronal invasion tendency has been recorded for almost all CoVs (Zhou *et al*. 2017). Given the similarities of the two strains, neurological disorders possibly caused by SARS-CoV-2 contribute substantially to developing acute respiratory failure. A 24-year-old Chinese patient with COVID-19 reported that he/she had to wake up to be able to breathe consciously because if he/she slept, he/she might lose his/her normal breath and die. Therefore, it is necessary to investigate the role of SARS-CoV-2 in acute respiratory failure of patients infected with COVID-19.

Hysteria, neuro-inflammation, and microglial activation

The CNS is highly protected against most viruses thanks to the blood-brain barrier (BBB), strong immune effectors, and external multilayer barriers. Despite this, various viruses can penetrate the central nervous system via the neural pathways or the circulatory system. The CNS or peripheral neural system infection is acquired and via axon transport mechanisms to reach the CNS. The infection may also be transmitted through circulatory cells from the blood-brain barrier (BBB) to the CNS (Koyuncu *et al*. 2013). In the haematogenous pathway, several viruses infect BBB endothelial cells or epithelial cells in the choroid plexus and thus attack nerve cells by passing through the BBB or hiding in leukocytes, so, can reach and replicate in the CNS (Koyuncu *et al*. 2013). As the virus passes through the CNS barriers and infects the tissue, microglia are activated as the first line of defence. Microglia are extremely heterogeneous mononuclear phagocytes localized in the brain (Saitgareeva *et al*. 2020) and serve different functions. They account for approximately 10% of all brain cells (Streit *et al*. 2004). Activated glial cells are involved in neuropathological conditions, which is also a sign of brain damage and neurological inflammatory response (Von Bernhardi *et al*. 2007). Microglia are not only capable of inducing immune responses in the brain, but also can react readily to external stimuli (Nakajima *et al*. 2001). Neuroprotective effects in the short term or damage to the nervous system in the long term depend on the balance of anti-inflammatory and pro-inflammatory cytokines released from microglia in reaction to infection with viruses (Koyuncu *et al*. 2013).

Table 1. Comparison of epidemiological, clinical and disease characteristics of SARS-CoV-2 with MERS-CoV and SARS-CoV.

Virus	MERS-CoV	SARS-CoV2	SARS-CoV
Host of virus	bats	Bats	bats
Transfer	Respiratory drops, Contact with an infected, patient or camel, Consumption of camel milk	Respiratory drops, Contact with an infected patient, Probably faecal-oral, Probably aerosol	Respiratory drops, Contact with an infected patient, Faecal-oral, Aerosol
Infection period	As long as the virus can be isolated from infected patients	Unknown	10 days after the onset of the disease
Enters host cells	dipeptidyl peptidase 4 (DPP4)	angiotensin-converting enzyme type 2 (ACE2) enzyme	-
Clinical symptoms	From asymptomatic or mild disease to acute upper respiratory tract disease and multiple organ failure leading to death. It varies between people. Vomiting and diarrhoea have also been reported.		
First identified location	Saudi Arabia (Jeddah)	Wuhan (China)	Guangdong (China)
Period	2012–ongoing	2019–present	2002–2003
Difference	Clinical symptoms emphasize differentiation; Confirmed cases depend only on etiology; no mention of imaging	Epidemiological history including clustered onset: Emphasis on peripheral blood test results	Clinical diagnosis emphasizes exclusion; Suspected cases may lack a clear epidemiological evidence

SARS-CoV2 neuro-invasive potential

This virus enters host cells by ACE2 enzyme, and ACE2 is present in human respiratory tract epithelium, lung parenchyma, vascular endothelium, cells of renal and small intestinal (Donoghue *et al*. 2000; Harmer *et al*. 2002; Hamming *et al*. 2004). Unlike SARS-CoV, the MERS-CoV virus enters host cells primarily through dipeptidyl peptidase 4 (DPP4) in the lower respiratory tract, cells of kidneys, small intestine, liver, immune system (Mattern *et al*. 1991; Boonacker *et al*. 2003). However, ACE2 and DPP4 are not sufficient for host cells to become infected, since some endothelial cells expressing ACE2 and human intestinal cell lines are not infected with SARS-CoV, while some cells without ACE2-detectable expression levels, such as hepatocytes, are infected with SARS-CoV (To *et al*. 2004). In one study, SARS-CoV and MERS-CoV infections were reported in the CNS, while ACE2 or DPP4 expression was very low under normal conditions (Netland *et al.* 2008; Bernstein *et al*. 2018). Studies on patients with SARS-CoV have confirmed the presence of SARS-CoV in the brain where nerve cells are present (Bernstein *et al*. 2018). Animal studies have also shown that when SARS-CoV and MERS-CoV are injected into the nose, they can enter the brain through the olfactory nerves and spread rapidly to certain areas. MERS-CoV particles were detected not only in the brain but also in the lungs, indicating a higher mortality rate in CNS infection (Bernstein *et al*. 2018). The exact route of CoV entry into the CNS has not yet been determined. The haematogenous or lymphatic pathway seems impossible, especially in the early stages of infection, since almost no virus has been detected in non-neuronal cells in infected brain areas. Evaluation of bronchitis in birds has demonstrated trans-synapse transmission of CoVs (Chasey *et al*. 1976). Neurotransmission of the virus through peripheral nerves to the medullary nerve cells responsible for the peristalsis of the gastrointestinal tract leads to nausea and vomiting (Mengeling *et al.* 1976; Andries *et al*. 1980). Noteworthy, antigens have been identified in the brainstem where the infected area is the solitary tract nucleus and the ambiguous nucleus. The solitary tract nucleus receives sensory information from mechanical and chemical receptors in the lungs and airways, and fibres transmitted from the ambiguus nucleus and the solitary tract nucleus provide neurotransmission to the smooth muscles of the airways, glands, and blood vessels (Mengeling *et al.* 1976). Influenza virus (IV) is the most frequently affecting virus of the respiratory system that can bring about neurological complications. Studies with animals have revealed that IV enters into the brain via lungs' vagal sensory neurons or the olfactory system (Mengeling *et al.* 1976). Respiratory viruses can gradually enter the brain by infecting the vagus nerve sensory fibres across various regions of the respiratory system. The vagus nucleus includes four nuclei, one of which is the nucleus ambiguus located in the BMO (Baker *et al*. 2020). COVID-19 may lead to respiratory failure and exacerbate the initial lung damage due to the infection through passing through the respiratory center in the brain via the vagus nerve. The viral brainstem infection starts from the vagus nucleus and peripheral regions (Baker *et*

al. 2020). In general, the neuro-invasive potential is a common feature in CoVs. Given the many similarities between COVID-19 and SARS-CoV, SARS-CoV2 may have a similar potential (Baker *et al*. 2020). A study of patients with COVID-19 found that about 88% of patients had acute neurological manifestations, including acute cerebrovascular disease and impaired consciousness. Thus, the knowledge of neuro-invasion is important in the prevention and treatment of SARS-CoV2-induced respiratory disorders (Rothe *et al*. 2020; Ansari *et al*. 2022). Corona virus (Karimi *et al*. 2021) are a group of viruses that cause damage to different parts of the body (Maroufi *et al*. 2016; Behroozi-Lak *et al*. 2017; Al-Awade *et al*. 2022; Jaber *et al*. 2022; Sulandjari *et al*. 2022), especially the respiratory system, and cause serious complications.

SARS-CoV-2 neuroinvasive potential Consequences

So far, no effective treatment has been presented for SARS-CoV2 as an emerging virus. Hence, awareness of the possible entry of SARS-CoV2 into the CNS is of great importance in prevention and treatment. Given the neuro-invasive effect of SARS-CoV2 on respiratory disorders in patients, wearing a mask is the most effective measure to protect against possible entry of the virus into the CNS. Patients infected through the oral or conjunctival tract are expected to have fewer clinical symptoms than patients infected through the nose. SARS-CoV2 neuro-invasion partly explains respiratory failure in patients. Hence, antiviral treatment should be performed as soon as possible to prevent the virus from entering the CNS. Inhalation of antiviral agents through the airways is the first choice in the early stages of the disease, which prevents the virus from multiplying in the respiratory tract and lungs and prevents neuro-invasion in the later stages of the disease. Moreover, corticosteroids, which are frequently used in acute patients, in addition to having no therapeutic effects, can cause the virus to multiply in nerve cells (Behroozi-Lak *et al*. 2017).

CONCLUSION

With regards to available evidence, CNS infection due to viral agents could result in respiratory dysfunctions that are not necessarily limited to the lung structure and therefore may be difficult to control. SARS-CoV2 is a neurotropic and neuro-invasive virus capable of causing neuropathological complications in vulnerable patients. Understanding the SARS-CoV2 neuro-invasive mechanisms is essential to understand the potential pathological relationship of infection and helps adopt interventional approaches to manage different virus-induced neurological disorders.

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