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Journal of Chemical Neuroanatomy 117 (2021) 102006

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

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

Can Covid-19 attack our nervous system?

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ARTICLE INFO

Keywords:
CNS
COVID-19
SARS-CoV-2

ABSTRACT

Nowadays, Covid-19 is considered a serious health problem worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human coronavirus that has sparked a global pandemic of the coronavirus disease of 2019 (COVID-19). It is well known that the Corona Virus attacks mainly the respiratory system. Meanwhile, it has been established that coronavirus infection can extend beyond the respiratory system and unfortunately, can also affect our nervous system. Multiple neurological symptoms and signs had been documented during and post covid conditions. This virus gets access to the central nervous system (CNS) *via* the bloodstream leading to infect the endothelial lining cells. Also, it was reported that the virus can enter the peripheral nervous system *via* retrograde neuronal routes. The virus could be internalized in nerve synapses through endocytosis, transported retrogradely, and spread trans-synoptically to other brain regions. This mini-review highlights the possible routes by which SARS-CoV-2 can invade the central nervous system (CNS) and its pathophysiology and manifestation.

1. Introduction

The emergence of SARS-CoV-2, the agent of novel coronavirus 2019 (COVID-19), has kept the globe in disquiets due to its severe life-threatening conditions (Achar and Ghosh, 2020; Mahalaxmi et al., 2021). This shattering disease of 2019 (COVID-19) is a pandemic infectious disease caused by SARS-CoV-2 (Organization, W.H., 2020). The first cases of COVID-19 were previously documented in December 2019 in Wuhan City, Hubei Province of China (Achar and Ghosh, 2020). After then, SARS-CoV-2 rapidly spread to over two hundred countries and territories (Rose-Redwood et al., 2020). Furthermore, the WHO reported COVID-19 as a global pandemic disease (Cucinotta and Vanelli, 2020). As of September 4, 2020, approximately twenty- six million cases of COVID-19 had been discovered, leading to ~860,000 deaths worldwide (Cucinotta and Vanelli, 2020). SARS-CoV-2 is well known as a human coronavirus; an enveloped, positive-sensed, ssRNA virus characterized by its crown-like shape (Ye et al., 2020). Even coronavirus (CoV) species are known as human pathogens; the epidemic viruses SARS-CoV, SARS-CoV-2, and MERS-CoV and those continuously circulating in human populations since initial isolation: HCoV-OC43, HCoV-229E, HCoV-HKU1, and HCoV-NL63. All lead to human central nervous system (CNS) dysfunction (Chen et al., 2020). In infants and young children, the most common CNS phenomena are febrile seizures; in adults, non-focal abnormalities may be either neurologic or constitutional (Morgello, 2020; Ye et al., 2020). Symptoms of COVID-19 range from mild to severe symptoms. Mild symptoms of COVID-19 including fever, chills, cough, dyspnea, fatigue, body aches, headache, loss of taste or smell, sore throat, congestion, nausea, and/or vomiting after two weeks of exposure to this virus (Ye et al., 2020). Severe signs from COVID-19 are in the form of pneumonia, acute respiratory distress syndrome, and sepsis (Jindal et al., 2020). It has been well-established that people who are more susceptible to severe illness include those aged people (Abdel Hafez, 2020). However, individuals of all ages are at a higher risk for severe illness if they suffer from any medical diseases or suffer from any comorbidities such as chronic lung, kidney, or liver disease, moderate to severe asthma, severe heart conditions, diabetes, severe obesity, and conditions that cause immunodeficiency (Thomé et al., 2020). It has been established that SARS-CoV-2 invades human cells through interaction with the human angiotensin-converting enzyme 2 (ACE2) receptor (Thomé et al., 2020). This mechanism is detailed in the section "Mechanism of Viral Invasion: ACE2 Receptor". As COVID-19 is primarily a respiratory disease, high levels of ACE2 have been observed in pulmonary type II alveolar cells and respiratory epithelial cells. While, ACE2 expression is not limited to the respiratory tract but extended to other areas that as myocardial cells, ileal and esophageal epithelial cells, renal proximal tubule cells, and bladder urothelial cells (Taatjes and Roth, 2016). So, the function and overactivity of the ACE2 receptor may influence such target cells and organs, increasing the susceptibility to infection (Thomé et al., 2020). Recently, some researchers had emerged of the neuro-invasive potential of this virus (Thomé et al., 2020).

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https://doi.org/10.1016/j.jchemneu.2021.102006
Received 29 April 2021; Received in revised form 17 July 2021; Accepted 18 July 2021
Available online 26 July 2021
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Previously, a retrospective performed study on COVID-19 patients in Wuhan, China, neurological symptoms were observed in 36.4 % of total patients and 45.5 % of patients with severe infections (Mao et al., 2020). The COVID-19 is more prevalent in human and has the prospect to reach the brain without evidence of clinical symptoms. Unfortunately, if there is any acute, tenacious or dormant form of viral infection inside the central nervous system, its immune system does not react subsequently, which results in neurological disorders. (Mahalaxmi et al., 2021). The symptoms of CNS infection included dizziness, headache, impaired consciousness, acute cerebrovascular disease, and ataxia (Tsivgoulis et al., 2020). However, a large-scale study of COVID-19 people from the United Kingdom revealed neurological disorders were frequent among the 153 "unique" cases of COVID-19 identified by physicians. Of the 125 patients with clinical data, a cerebrovascular event, defined as ischemic stroke, intracerebral hemorrhage, or CNS vasculitis, was observed in 62 % of patients reported. An altered mental status, defined as unspecified encephalopathy, encephalitis, or psychiatric diagnosis, was observed in 31 % of patients (Varatharaj et al., 2020). Additionally, the presentations of COVID-19-associated multiple neurological disorders were observed to fit into five distinct categories such as encephalopathies, inflammatory CNS syndromes, ischemic strokes, peripheral neurological disorders, and miscellaneous other CNS disorders (Paterson et al., 2020). As the neurological manifestations had become increasingly prevalent recently, some evidence detected that illness from COVID-19 may go beyond that of respiratory tract infectivity. Moreover, according to the anecdotal researches from the health care workers, it had been reported that the COVID-19 could reach the CNS with subsequently leads to anosmia, hyposmia, hypogeusia, and hyposmia. Once the SARS- CoV-2 has attacked the CNS, it could either exit in an inactive form in the cells or might lead to inflammation of the nervous tissue. (Mahalaxmi et al., 2021). This minireview highlights the possible routes by which SARS-CoV-2 may invade CNS and its pathophysiology and manifestations.

2. Basic biology of coronaviruses

Coronaviruses are a large expanding family of membrane-enveloped, positive sense, single-strand RNA viruses, with genomes ranging in molecular weight from 25 to 32 kb. They are roughly about 120–140 nm in diameter, inclusive of spike (S) proteins that protrude from their envelopes to a height of approximately 20 nm, producing the corona-like appearance appeared by electron microscopic study that gives the family this name (Morgello, 2020). Within the subfamily Coronavirus, there are 4 geniuses included alpha, beta, gamma, and delta defined by intra-genus conservation of seven domains in the viral replicase/transcriptase; within each genus, species are defined by a minimum of 90 % amino acid sequence homology in these conserved regions (Perlman and Masters, 2020).

Currently, exceptionally, mammalian coronaviruses are members of the alpha and beta genesis. The global distribution of coronavirus species is "driven" by bat populations, which constitute the major viral reservoir. In regions of the world where bats are highly diverse, as in portions of Asia and Africa, host switching is the dominant mechanism of viral evolution (Anthony et al., 2017). Thus, zoonotic transmission to man was a higher probability in these geographic areas, like host switching is its predicate. There are currently 7 known human coronaviruses; almost all have zoonotic origins or are known to circulate in animals (Anthony et al., 2017). Animal surveillance had been suggested as a useful technique in combatting epidemic viruses as, both SARS-CoV and SARS-CoV-2 could infect as well replicate in domestic cats, with transmission from infected to uninfected cats occurring through respiratory droplets (Anthony et al., 2017). As these common pets may be in the community as well as in close contact with their owners at home, they may conceivably provide an adjunctive mechanism for virus tracking.

3. Pathophysiology of coronavirus

SARS-CoV-2 is a highly pathogenic coronavirus that had led to ongoing worldwide pandemic disease (Sharma et al., 2020). One of the earliest symptoms reported in covid is loss of smell. It was reported that the virus could access to the central nervous system through the bloodstream with subsequently leads to endothelial cell infection. Additionally, the virus can enter the peripheral nervous system through retrograde neuronal routes (Abdullahi et al., 2020). This virus may internalize into the nerve terminals *via* endocytosis, transported retrogradely, and widely spread trans-synoptically to other brain areas (Iadecola et al., 2020).

Angiotensin-converting enzyme -2 receptor; was observed in the nasal mucosal lining; is attacked by the virus. The presence of these receptors in the tissues of the central nervous system is hypothesized to be the reason that the virus subsequently leads to neurological symptoms and signs (Moreno et al., 2004). After the virus goes to the cerebral circulation, its protein S protein interacts with the capillary endothelium ACE-2 receptors. After then, the virus buds from the capillary endothelium leading to the widespread of the virus in multiple areas of the brain and brainstem through the Virchow-Robin spaces surrounding both the arterioles and venules (Iadecola et al., 2020). Cytokine Storm is another mechanism responsible for neurological manifestations in coronavirus infection. This storm leads to dysfunctional, uncontrolled, continuous activation of inflammation. Finally, inflammation is proposed strongly to link stress to stress-related diseases, and multiple types of research documented that excessive inflammation is directly involved in the pathophysiology of stress-related disease (Elbassuoni and Abdel Hafez, 2019; Hafez et al., 2020). There is evidence that inflammation leads to subsequent acute respiratory distress syndrome, renal failure, myocardial injury, the severity of illness, the requirement of intensive care unit admission, lately, the requirement of mechanical ventilation, and mortality. The presence of inflammatory markers like C-reactive protein and leukocytes confirm the presence of cytokine storm.

CNS receptors for epidemic viruses are largely expressed on brain vasculature, whereas receptors for less pathogenic viruses are present in the vasculature, brain parenchyma, and olfactory neuroepithelium, dependent upon viral species (Wiley et al., 2015). Human coronaviruses can infect the circulating monocytes and lymphocytes, but meningoencephalitis is rare. Well-documented human neuropathologies are infrequent and, for SARS, MERS, and COVID-19 can entail cerebrovascular accidents originating extrinsically to the brain. There is evidence of neuronal infection in the absence of inflammatory infiltrates with SARS-CoV, and cerebrospinal fluid studies of rare patients with seizures have demonstrated virus but no pleocytosis. Meanwhile, to human disease, animal models of neuropathogenesis are well developed, and pathologies including demyelination, neuronal necrosis, and meningoencephalitis are seen with both native CoVs as well as human CoVs inoculated into nasal cavities or brain (Morgello, 2020).

4. Neurological manifestations

It was decomented that the major clinical manifestations of SARS-CoV-2 infection are respiratory due to pulmonary complications. Symptoms can be mild, including fever, headache, cough, dyspnea, and myalgia; or severe, such as acute respiratory distress syndrome (ARDS), which sometimes develops about 1 week into the illness and may result in death. CNS complications of COVID-19 infection have not been systematically investigated or analyzed (Khateb et al., 2020).

Additional neurological signs, documented in patients with severe SARS-CoV-2 with ARDS include myalgia (Munhoz et al., 2020), diffuse corticospinal tract signs with enhanced tendon reflexes and ankle clonus, and dysexecutive syndrome. Other signs, imaging findings included perfusion abnormalities in all the patients, leptomeningeal enhancement in most of them, and cerebral ischemia in about 23 %. Meanwhile, these results should be interpreted cautiously, as they could

represent, at least in part, different effects of the critical illness state, regardless of the SARS-CoV-2 etiology (Khateb et al., 2020).

5. Conclusion

This minireview highlights the possible routes by which SARS-CoV-2 can invade the central nervous system (CNS) and its pathophysiology and manifestation. This virus gets access to the central nervous system (CNS) *via* the bloodstream leading to infect the endothelial lining cells. Also, it was reported that the virus can enter the peripheral nervous system *via* retrograde neuronal routes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors report no declarations of interest.

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