Review Paper: COVID-19 and Central Nervous System: Entry Routes And

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ABSTRACT

Awareness of the current outbreak of Coronavirus Disease - 2019 (COVID-19) affecting the nervous system and identifying its possible ways to enter the Central Nervous System (CNS) are critical for the prevention and treatment of the disease. Hence, the CNS implications of the COVID-19 since the spread of the virus were reviewed in this study.

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Highlights

- Neuronal pathway, angiotensin-converting enzyme and blood circulation pathway are the most obvious pathways for SARS-CoV-2 to enter the CNS.
- Hypoxia and immune injury are the most important injuries caused by COVID-19.
- Cognition impairment is one of the problems in patients infected by COVID-19.

Plain Language Summary

Covid-19 disease, which is caused by human infection with a type of coronavirus called SARS-CoV-2, is usually characterized by symptoms such as fever, dry cough, and sometimes respiratory problems. Recent research has shown that in more than 2% of patients, in addition to the respiratory system, infection also occurs in the nervous system. SARS-CoV-2 can pass the protective structures and therefore travel to the nervous system through pathways that are not yet well known. One of the most likely ways is through the nose. In the upper part of the nose, there are mucous layers that contain olfactory receptor cells. These receptor cells interact directly with olfactory neurons in the brain. The olfactory pathway, thereby delivers olfactory messages to the brain. If a person is exposed to an infected environment and the coronavirus enters his or her nose after inhalation, it is possible that the virus may spread through the olfactory mucosa to the central nervous system and cause brain infection. As a result of the damage that viruses cause to the respiratory system, the efficiency of this system for exchanging the respiratory gases will reduce, and subsequently, the amount of oxygen in the blood will reduce. The lack of oxygen in the blood can also lead to impaired brain function. Symptoms of neurological damage in patients with COVID-19 include headache, loss of consciousness, decreased sense of taste and smell, tingling in the limbs, and cerebrovascular disorders. Impaired nervous system and brain function might have long-term effects, and these effects may be seen in the patients even after the symptoms of the disease have improved. It is recommended to wear a mask during the spread of the disease to prevent the virus entry to the central nervous system through the respiratory system. Any disorders related to brain function in these patients should be taken very seriously and the necessary medical advice should be provided in this regard.

1. Introduction

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019, and then has spread globally (Thompson, 2020). Coronaviruses (CoVs) are positive-sense single-stranded RNA viruses, with a genome of about 26-32 kb, an average diameter of 100 nm, and crown-like membrane glycoproteins on the surface (Schoeman & Fielding, 2019; Corman, Lienau, & Witzenrath, 2019b).

The neurological symptoms, including headache, disturbed consciousness, cognition impairment, and paresthesia have been reported in 36.4% of the COVID-19 patients. The development of these symptoms is dependent on the severity of disease so that the severely distressed patients are more susceptible to promote neurological symptoms (Mao et al., 2020). Moreover, brain tissue edema and partial neuronal degeneration have also reported in the expired patients' autopsy (Xu et al., 2020). The genome sequencing revealed the existence of SARS-CoV-2in the Cerebrospinal Fluid (CSF) of affected people, which demonstrates that COVID-19 has the potential to damage the nervous system (Wu et al., 2020b). There are six types of CoVs known as pathogenic viruses that cause severe diseases in humans (human coronaviruses (HCoV), including SARS-CoV, Middle East Respiratory Syndrome (MERS)-CoV, HCoV-HKU1, HCoV-NL63, HCoV-OC43, and HCoV-229E. COVID-19 pneumonia has caused by SARS-CoV-2 , as the seventh known CoV, that infects humans (Corman et al., 2019a). The most prevailing and important types of CoV infections with potential nervous system involvement are briefly explained below.

1.1. SARS-CoV

SARS-CoV that causes Severe Acute Respiratory Syndrome (SARS) was first identified in Asia in 2003, and then has spread throughout the world. The most common symptoms of SARS are fever, chills, dry cough, and diffi-

culty in breathing. Besides, respiratory failure and death may happen in severe cases (Lai, Tsang, Seto, & Ooi, 2004). Polyneuropathy, encephalitis, and aortic ischemic stroke are prevalent reported neurological diseases caused by SARS-CoV (Tsai, Hsieh, & Chang, 2005).

1.2. MERS-CoV

MERS-CoV resulted in Middle East Respiratory Syndrome (MERS) in 2012. MERS originated from bats, and then transferred to humans through the camels, as an intermediate host. Patients with MERS usually experience pneumonia-related symptoms, including fever, myalgia, cough, and dyspnea. Severe cases have been reported with Acute Respiratory Distress Syndrome (ARDS), septic shock, multiple organ failure, and death. The neurological symptoms, such as disturbance of consciousness, paralysis, ischemic stroke, and Guillain-Barre syndrome also have announced in almost 1/5 of the MERS patients. Interestingly, these neurological symptoms usually appear 2-3 weeks after respiratory symptoms (Kim et al., 2017).

1.3. SARS-CoV-2

SARS-CoV-2 is genetically 79.5% similar to SARS-CoV, and its similarity to MERS-CoV is as high as 96% (Wu et al., 2020a, 2020b). The clinical data have revealed the presence of symptoms similar to intracranial infections, such as headache, disturbed consciousness, and epilepsy in COVID-19 patients. Furthermore, anosmia and ageusia might also occur in these patients because of a sudden loss of smell or taste reported in the number of COVID-19 patients (Giacomelli et al., 2020; Hopkins & Kumar, 2020). Recently, a case of viral encephalitis caused by SARS-CoV-2 reported in Beijing Ditan Hospital. Subsequent genome sequencing confirmed the presence of SARS-CoV-2 in the CSF of this patient, which further supports the nervous system damage theory by this new CoV (Xiang, Xu, Gao,Wang, Xiong, & Li, 2020).

2. Probable Pathways to Enter the CNS

2.1. Neuronal pathway

One of the key pathways for neurotropic viruses to enter the CNS and damage the nervous system is infecting sensory or motor nerve endings and achieving retrograde or anterograde neuronal transport through the motor proteins, dynein, and kinesins (Swanson & McGavern, 2015). The olfactory neuron transport is one of the neuronal pathways for virus entry to the CNS. The unique anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain effectively represent it as a channel between the nasal epithelium and the brain compartments, especially the brainstem (Koyuncu, Hogue, & Enquist, 2013). As a consequence, the presence of the virus in the brainstem can damage the neurons involved in the regulation of respiration and cardiovascular activity, resulting in lung function failure (Steardo, Steardo, Zorec, & Verkhratsky, 2020; Netland, Meyerholz, Moore, Cassell, & Perlman, 2008b). Therefore, CoV can reach the brain structures using the olfactory tract in the early stages of infection or nasal vaccination and make inflammation and demyelinating reaction (Desforges, Le Coupanec, Dubeau, Bourgouin, Lajoie, Dubé, & Talbot, 2020; Mori, 2015). In this regard, Bohmwald et al. showed that olfactory bulb removal limited the invasion of CoV into the CNS in mice (Bohmwald, Galvez, Ríos, & Kalergis, 2018).

It has been hypothesized that the virus could spread into the olfactory bulb and other brain structures, especially the medulla oblongata in the brainstem through infecting the olfactory receptors in the neuroepithelium leading to acute respiratory failure. In this regard, Ceccarelli et al. using transgenic mice showed that the intranasal administration of SARS-CoV, which shares similarities with SARS-CoV-2, could enter the brain via the olfactory nerves and spread into the thalamus and brainstem (Ceccarelli, Berretta, Venanzi Rullo, Nunnari & Cacopardo, 2020). On the other hand, infection of the brainstem with the virus may impair the chemosensing neural cells associated with respiratory and cardiovascular centers, which disturbs the lung ventilator action. Clinical observation revealed the occurrence of anosmia in SARS-CoV-2-infected patients, which can confirm that the nasal route may contribute to the entry of the virus into the brain (Gandhi, Srivastava, Ray, & Tripathi, 2020).

2.2. Angiotensin-converting enzyme 2

Angiotensin-converting Enzyme 2 (ACE2), a cardiocerebral vascular protection factor, is reported as an important target for CoV and influenza virus (Turner, Hiscox, & Hooper, 2004). This enzyme presents in the nervous system and skeletal muscles and has an important role in blood pressure regulation and anti-atherosclerosis mechanisms (Miller & Arnold, 2019). In the brain, the ACE2 receptors have been detected in the glial cells and neurons, particularly in the brainstem and the regions responsible for the regulation of cardiovascular function, including subfornical organ, paraventricular nucleus, nucleus tractus solitarius, and rostral ventrolateral medulla, making them a potential target for COVID-19 (Gowri-

sankar & Clark, 2016; Xia & Lazartigues, 2010). It has been reported that SARS-CoV-2, like SARS-CoV, attaches to the cell membrane by interacting with the host ACE2 receptor using a spike protein S1 (Netland et al., 2008a). Moreover, the binding affinity of ACE2 for the SARS-CoV-2 spike protein is reported 10–20-fold higher than the affinity for the SARS-CoV spike protein (Wang et al., 2020). Therefore, the virus binding to the ACE2 receptors can lead to high blood pressure and cerebral hemorrhage. Moreover, because SARS-CoV-2 spike protein can interact with ACE2 expressed in the capillary endothelium, the virus may also enter the CNS through attacking the vascular system and damaging the Blood-Brain Barrier (BBB) (Baig et al., 2020).

2.3. Blood circulation pathway

One of the known viruses affecting CNS through the blood circulation pathway is the Japanese encephalitis virus that transmits to the blood after being bitten by a mosquito. After reproducing in the skin vascular cells, the virus multiplies in the macrophages through the body. Thereafter, the secondary release of the virus into the blood may enhance the permeability of the BBB via the produced cytokines, stimulating the virus to enter the brain, and causing viral encephalitis (Unni, Růžek, Chhatbar, Mishra, Johri, & Singh, 2011). There are a few pieces of evidence regarding CoVs, especially SARS-CoV-2 to be entered the nervous system via the blood circulation pathway (Desforges et al., 2020); hence, further studies are required.

3. The Most Important Injuries Caused by Cov

3.1. Hypoxia injury

The proliferation of a virus in lung tissue cells is accompanied by alveolar gas exchange disorders causing hypoxia in the CNS and enhancing anaerobic metabolism in the brain cells' mitochondria (Abdennour, Zeghal, Dème, & Puybasset, 2012). Brain hypoxia subsequently may cause cerebral vasodilation, brain cells swelling, interstitial edema, cerebral blood flow obstacle, and even headache due to ischemia and congestion (Abdennour et al., 2012). In the persistent hypoxia, reduced brain function can be followed by drowsiness, bulbar conjunctival edema, and even coma (Abdennour et al., 2012). In addition, hypoxia may also induce acute ischemic stroke in patients with a particular risk of developing the cerebrovascular disease. Because the patients with COVID-19 often suffer from severe hypoxia (Guo et al., 2020); therefore, hypoxia injury may result in subsequent nervous system damage.

3.2. Immune injury

A large number of SARS and COVID-19 reported deaths have happened due to multiple organ failure caused by virus-induced Systemic Inflammatory Response Syndrome (SIRS) or SIRS-like immune disorders (Chen, Zhang, Ju, & He, 2020). A neurotropic virus can cause chronic inflammation and brain damage through the activation of glial cells, and subsequently a massive production of inflammatory factors, such as cytokines, chemokines, and other inflammation signals. The produced inflammatory signals, then lead to a significant break of BBB, which provokes and magnifies the neuroinflammatory process (Wang et al., 2020b). Bohmwald et al. showed that primary glial cells cultured in vitro secrete Interleukins (ILs), including IL-6, IL-12, IL-15, and Tumor Necrosis Factor-alpha (TNF)-α after being infected with CoV (Bohmwald et al. 2018). Additionally, the positive correlation between IL-6 and the severity of COVID-2019 symptoms has been reported (Wan et al., 2020).

3.3. Cognition impairment

Numerous preclinical and clinical studies have provided evidence that systemic inflammation can perturb brain homeostasis and cause neuronal death. The bacterial, viral, and toxic inflammation can damage glia limitans, activate Toll-like receptors in microglia and astrocytes, and eventually promote neuroinflammation that may result in cognitive impairments (Sankowski, Mader, & Valdés-Ferrer, 2015). Neuroinflammation induced by systemic inflammation associated with prolonged hypoxia damages brain regions responsible for cognitive functions and behavioral alterations, such as the hippocampus and cortex (Sasannejad, Ely, & Lahiri, 2019). Hence, the functional brain damage can describe the deficits in delirium, attention, and memory in aged patients overcoming pneumonia. Delirium is commonly triggered by peripheral infection associated with systemic inflammation and is accompanied by an elevated level of serum pro-interleukins and S100B (as an index for BBB disruption) in elderly patients (McNeil et al., 2019). Neuroinflammation has been implicated as an almost obligatory factor in neurodegenerative disorders (Heneka et al., 2015) and psychiatric pathologies, including acute psychosis, schizophrenia, and autism spectrum disorder (Pape, Tamouza, Leboyer, & Zipp, 2019).

There is a strong association between systemic inflammation and depressive syndromes so that infections enhance the risk of depressive episodes by ~60%. In animal models, injections of cytokines stimulated sickness behavior similar to a human "flu-like syndrome" characterized by anhedonia, anorexia, fever, fatigue, increased pain, sleep distur-

bances, and confusion (De La Garza, 2005). Besides, severe respiratory failure accompanying COVID-19 prompts long-lasting hypoxia, which arguably affects the brain and leads to neurocognitive impairments.

4. Conclusion

The brainstem, as one of the most important areas of the brain involved in infection with CoVs, has a pivotal controlling action on the respiratory, cardiac, and vascular systems. Therefore, the spread of respiratory failure and death of patients with the COVID-19 may be due to the weakened performance of cardiovascular and respiratory centers in the brainstem. Because the most probable route for viruses to enter the nervous system is the nasal epithelium, wearing a face mask can be effective to protect against virus entry into the CNS. On the other hand, regarding the COVID-19 neuroinvasive potential, further studies are needed to find effective antiviral drugs being able to cross the BBB.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors' contributions

Original idea, wrote initial topics and headlines, and the first draft: Nooshin Ahmadirad; Participated in the writing, editing, and final revision of the manuscript: Zahra Ghasemi.

Conflict of interest

The authors declare no conflict of interest and declare that this work was accompanied with no commercial or financial relationships that could be construed as a potential conflict of interest.

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