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The involvement of the central nervous system in patients with COVID-19

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Abstract: Coronaviruses disease (COVID-19) has caused major outbreaks. A novel variant, SARS-CoV-2, is responsible for COVID-19 pandemic. Clinical presentations and pathological mechanisms of COVID-19 are broad. The respiratory aspect of the disease has been extensively researched. Emerging studies point out the possibility of the central nervous system (CNS) involvement by COVID-19. Here, we discuss the current evidence for CNS involvement in COVID-19 and highlight that the high pathogenicity of SARS-CoV-2 might be due to its neuro-invasive potential.

Keywords: ACE2; anosmia; central nervous system (CNS); coronavirus; COVID-19; SARS-CoV-2.

Introduction

Coronaviruses (CoVs) are enveloped viruses that comprise a positive-sense single-strand RNA genome. Human CoVs (HCoV) have the potential to affect the respiratory and central nervous system (CNS) and cause a variety of symptoms. HCoVs, including, HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63, have spread

globally and mainly cause mild symptoms. There are HCoVs that cause severe illness including, severe acute respiratory syndrome CoV (SARS-CoV), Middle East respiratory syndrome CoV (MERS-CoV), and the recent SARS-CoV-2, which has been caused a pandemic of coronavirus disease 2019 (COVID-19). The respiratory clinical features of the disease, like bronchitis and pneumonia, have been adequately addressed. However, the coexistence of CNS symptoms with these common symptoms is less understood (Li et al. 2016; Matoba et al. 2015).

History of the involvement of CNS by hCoV

The involvement of the CNS by CoVs dates back to the 1980s. Two CoVs isolated from patients with multiple sclerosis (MS) were neutralized using the patients' serum. It indicates that CoVs may play a vital role in the etiology of MS (Burks et al. 1980). At that time, limited laboratory techniques may have prevented further investigations on this phenomenon. For instance, the polymerase chain reaction (PCR) technique was first introduced in 1985 and has been one of the most commonly used techniques for the detection of viral RNA since its introduction.

CNS manifestations in SARS-CoV, MERS-CoV, and SARS-CoV-2 infections

MERS-CoV

The evidence points out the possibility of CNS involvement by virulent HCoVs, including SARS-CoV, MERS-CoV, and SARS-CoV-2. In 2015, the first cases of MERS-CoV with CNS symptoms were reported. A 74-year-old patient was admitted to the hospital with a history of contact with camels and a possible stroke. Repeated brain computed tomography (CT) scans showed patchy hypodensities. Interestingly, the patient showed a white cell count of 1 cell

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and a protein of 0.56 g/l in cerebrospinal fluid (CSF). Also, the patient had a negative CSF MERS-CoV real-time (RT)-PCR (Arabi et al. 2015).

SARS-CoV

The CNS symptoms of SARS-CoV were first revealed in 2016 when a study reported clinical features of 183 children with acute encephalitis-like syndrome and 236 children with respiratory infections. Some suspected cases with encephalitis were diagnosed with CoV infection. Common symptoms included fever, headache, and vomiting. Most patients were males with an average age of three years old. Neuroimaging abnormalities occurred in 50% of patients and involved the temporal lobe, periventricular region, basal ganglia, and thalamus. The CSF analysis of patient subgroups showed pleocytosis, normoglycorrhachia, and hyper proteinorachie. CNS-CoV cases demonstrated lower levels of lymphocytes, eosinophils, and higher levels of neutrophils compared with respiratory-CoVs and healthy controls. Besides, significantly higher levels of monocytes were found in CNS-CoV cases compared with healthy controls. Serum GM-CSF levels of cases infected with CNS-CoVs exceeded those of respiratory-CoVs, healthy controls, and paired cerebrospinal fluid specimens. CNS-CoV patients had higher levels of IL-6, IL-8, and MCP-1 in the CSF than serum specimens (Li et al. 2016).

SARS-CoV-2

A recent case of COVID-19 was a middle-aged male, presented with viral encephalitis, a normal skull CT scan, and a positive CSF RT-PCR for SARS-CoV-2 (Jingwei 2020). Also, a study that screened neurological symptoms in COVID-19 patients included 214 patients, among whom 41.1% had a severe form of the disease, and the remainder presented non-severe symptoms of the infection. Neurological symptoms were reported by 36.4% of patients and were classified into three sub-categories: CNS, peripheral nervous system (PNS), and muscular-skeletal symptoms. Importantly, these investigations revealed that CNS and musculoskeletal symptoms were considerably higher in the severe group. For example, acute cerebrovascular illnesses occurred in five cases in the severe group compared to one case in the non-severe group. Also, consciousness impairment presentations were observed in 13 cases in the severe group compared to three cases in the non-severe group (Mao et al. 2020). This clinical data highlights the

significance of CNS involvement in patients with COVID-19, particularly in severe phases of the disease.

Implications of CNS involvement by SARS-CoV2

CNS involvement in COVID-19 is of crucial importance, as it might affect the disease severity, clinical presentations, and frequency of symptoms. In particular, CNS involvement may worsen the respiratory situation in patients with SARS-CoV-2. The neuroinvasion of SARS-CoV-2 might explain why some patients are developed respiratory failure, while others do not.

There has been a rising debate on the neuroinvasive pathways responsible for various CoVs. Human and animal studies have shown the ability of SARS-CoVs to infect the brains, and in particular, the brain stem. Some CoVs can spread via axons to the medullary, originating from mechanoreceptors and chemoreceptors in the lung and lower respiratory airways.

Mechanisms of CNS involvement by SARS-CoV2

Similar to other respiratory infections, SARS-CoV-2 may invade the CNS via a hematogenous or retrograde neuronal pathway. The second can be supported by the evidence that several cases in a relatively large study group were diagnosed with hyposmia. Diagnostic value of hyposmia was recently measured in combination with hypogeusia. The study reported that the optimal criteria could be reached via combining both hypogeusia and hyposmia while showing no signs of ear, nose, and throat (ENT) disorders. Results indicated a specificity of 95% (95% CI 90–98) and a sensitivity of 42% (95% CI 27–58). However, the study was considerably limited by small patient population, no collection of demographic data, relying on self-report, and the conduction of the study among patients with positive nasopharyngeal sample RT-PCR which has shown relatively unfavorable sensitivity (in some cases as low as 60%) (Bénézit et al. 2020). Change in the sense of smell has been reported in mild cases of COVID-19. For instance, a recent study utilized Sino-nasal Outcome Test 22 (SNOT-22), which is an objective questionnaire for evaluation of sense of smell, and reported that out of 202 included cases with positive RT-PCR nasopharyngeal specimen, 130 experienced some degree of hyposmia during the 14 days before RT-PCR testing (Spinato et al.

2020). Also, for SARS-CoV-2, angiotensin-converting enzyme (ACE) 2 has been declared to regulate a potential mechanism of the neuroinvasive features of the virus, a pathway similar to what has been described for SARS-CoV (Figure 1). A case report of a non-traveler from Japan first suggested the association of meningitides and encephalitis with COVID-19 (Moriguchi et al. 2020). Another recent case report from Wuhan further reported that self-limited encephalitis, along with myalgia, fever, and consciousness deterioration, may be found in COVID-19 patients despite negative Ig M/G for CSF specimen (Ye et al. 2020). However, Interestingly, animal models have shown that neuroinvasive pathways may cause a neuronal loss in the absence of encephalitis. HCoV-NL63 also acts through ACE2-mediated cell entry but causes mild symptoms. It shows that additional factors play a role in the pathogenicity of virulent HCoV (Hofmann et al. 2005). The transfer of the COVID-19 virus to the cerebrum via the cribriform plate near the olfactory bulb may act as an additional pathway that could induce the virus to get into, and as a result, influence the brain. The clinical features, such as a changed sense of smell or hyposmia in an uncomplicated early stage of COVID-19 patients, should be investigated precisely.

Conclusions

COVID-19 has been a challenge for the globe. Case reports and case-series highlight the presence of various CNS-related symptoms in patients with COVID-19. The more frequency of CNS-related symptoms in patients with severe than mild-to-moderate COVID-19 indicates that high pathogenicity of SARS-CoV2 might be due to its neuroinvasive potential. The candidate pathways identified for the neuroinvasive behavior of the infection include olfactory and ACE-related routes. Comprehending the multifaceted pathophysiology of COVID-19 may pave the path for overcoming the pandemic through shifting the therapeutic approach toward combined CNS and respiratory treatment of SARS-CoV-2, which may lead to more effective drug discovery results. Cost-effectiveness and diagnostic potential of newly surfaced criteria, such as neurological symptoms in individuals with contact history with SARS-CoV-2 positive patients, and taste and smell dysfunction, should be further studied in larger prospective studies. By considering the neurological manifestations of the disease, there is a need for the development of a staging system for COVID-19 (Baig et al. 2020; Netland et al. 2008). Also, novel detection tools are necessary to improve understanding of

Figure 1: Potential neuroinvasive mechanisms of SARS-CoV-2 and associated imaging abnormalities. Pathways that may be responsible for the neuroinvasive capability of SARS- and MERS-CoV are demonstrated briefly. Neuronal damage induced by SARS-CoV-2 may act through docking on ACE 2 receptors. This novel CoV may function through pathways, similar to that of SARS-CoV. Moreover, hematogenous dissemination facilitates tissue tropism. (A) (I) SARS-CoVs can infect neurons via a retrograde transsynaptic route via ACE 2 receptors, (II) infecting the thalamus and brain stem considerably. (B) Further, MERS-CoV binds to dipeptidyl peptidase (DPP4), which is known as the MERS-CoV receptor. Both SARS- and MERS-CoVs invade the lung following respiration. (C) (I) Temporal lobe, (II) basal ganglia, and periventricular region abnormalities have been found in the imaging of COVID-19 patients. These regions are similar to SARS-CoV infection areas.

the interplay between the involvement of CNS and other organs by COVID-19.

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References

- Arabi, Y. M., Harthi, A., Hussein, J., Bouchama, A., Johani, S., Hajeer, A. H., Saeed, B. T., Wahbi, A., Saedy, A., AlDabbagh, T., et al. (2015). Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 43: 495–501.
- Baig, A. M., Khaleeq, A., Ali, U., Syeda, H., (2020 Mar 13). Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem. Neurosci.* 11: 995–998.
- Bénézit, F., Le Turnier, P., Declerck, C., Paillé, C., Revest, M., Dubée, V., Tattevin, P., Arvieux, C., Baldeyrou, M., Chaplain, J.-M., et al. (2020 Apr 15). Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect. Dis.* [https://doi.org/10.1016/S1473-3099\(20\)30297-8](https://doi.org/10.1016/S1473-3099(20)30297-8).
- Burks, J. S., DeVald, B. L., Jankovsky, L. D., and Gerdes, J. C. (1980). Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. *Science* 209: 933–934.
- Hofmann, H., Pyrc, K., van der Hoek, L., Geier, M., Berkhout, B., and Pöhlmann, S. (2005). Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc. Natl. Acad. Sci. U.S.A.* 102: 7988–7993.
- Jingwei, S., (2020). Beijing Ditan Hospital warns novel coronavirus could attack central nervous system. <https://news.cgtn.com/news/2020-03-05/The-novel-coronavirus-could-attack-the-central-nervous-system-OBFZSvrn2g/index.html>.
- Li, Y., Li, H., Fan, R., Wen, B., Zhang, J., Cao, X., Wang, C., Song, Z., Li, S., and Li, X. (2016). Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. *Intervirology* 59: 163–169.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., et al., (2020 Apr 10). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *J. Am. Med. Assoc. Neurol.* <https://doi.org/10.1001/jamaneurol.2020.1127>.
- Matoba, Y., Abiko, C., Ikeda, T., Aoki, Y., Suzuki, Y., Yahagi, K., Matsuzaki, Y., Itagaki, T., Katsushima, F., Katsushima, Y., et al. (2015). Detection of the human coronavirus 229E, HKU1, NL63, and OC43 between 2010 and 2013 in Yamagata, Japan. *Jpn. J. Infect. Dis.* 68: 138–141.
- Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., Ueno, M., Sakata, H., Kondo, K., Myose, N., et al. (2020). A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94: 55–58.
- Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., and Perlman, S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J. Virol.* 82: 7264–7275.
- Spinato, G., Fabbri, C., Polesel, J., Cazzador, D., Borsetto, D., Hopkins, C., Boscolo-Rizzo, P., (2020 Apr 22). Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *J. Am. Med. Assoc.* <https://doi.org/10.1001/jama.2020.6771>.
- Ye, M., Ren, Y., and Lv, T. (2020). Encephalitis as a clinical manifestation of COVID-19. *Brain Behav. Immun.* S0889-1591: 30465–30467.