





SARS-CoV-2 invasion of the central nervous: a brief review

Ruqaiyyah Siddiqui ^a, Mohammad Ridwane Mungroo ^b and Naveed Ahmed Khan^b

^aCollege of Arts and Sciences, American University of Sharjah, University City, Sharjah, United Arab Emirates; ^bDepartment of Clinical Sciences, College of Medicine, University of Sharjah, University City, Sharjah, United Arab Emirates

ABSTRACT

There is increasing evidence of the ability of the novel coronavirus to invade the central nervous system (CNS). But how does a respiratory virus invade the highly protected CNS? Here, we reviewed available literature and case reports to determine CNS involvement in COVID-19, and to identify potential regions of the brain that may be affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its possible route of entry into the brain to identify its pathogenicity. Based on the symptoms, the parietal lobe and the cerebellum are the likely targets of SARS-CoV-2; however, further work is needed to elucidate this. The presence of ACE2, used by SARS-CoV-2 for cell entry, in the brain as well as detection of the virus in the cerebrospinal fluid, further assert that SARS-CoV-2 targets the brain, and therefore, medical practitioners should take that into account when dealing with patients suffering from COVID-19.

ARTICLE HISTORY

Received 22 October 2020
Accepted 5 February 2021

KEYWORDS

SARS-CoV-2; coronavirus; COVID-19; 2019-nCoV; brain; central nervous system; encephalitis



1. Introduction

The coronaviruses, comprising the severe acute respiratory syndrome coronavirus (SARS-CoV), human coronavirus NL63 (HCoV-NL63), Middle East respiratory syndrome-CoV (MERS-CoV), HCoV-OC43, HCoV-HKU1, and HCoV-229E amongst others, are a family of ribonucleic acid viruses that are known to cause disease in humans and animals [1–8]. The recently elucidated SARS-CoV-2, is the seventh affiliate of the coronavirus family and has infected over 96.9 million people (as of 21 January 2021) since its discovery in December 2019 [1,9]. Three strains of SARS-CoV-2 have been reported based on amino-acid changes, namely A, B, and C. Type A is the ancestral type, and C type is found globally, while B is mostly found in East Asia [10]. While SARS-CoV-2 is primarily recognized to affect the respiratory system, there is growing evidence that it also invades the central nervous system (CNS). SARS-CoV as the predecessor of SARS-CoV-2 has been shown to infect the brain, and it has been identified in neurons of the brain [11]. This is concomitantly with previous studies that reported that CNS infection with MERS-CoV was more pivotal with higher mortality rates as compared to lung infections [12]. SARS-CoV has also been identified in brain tissues with focal degeneration of neurons and edema, while infection of neurons was confirmed through *in situ* hybridization, electron microscopy, and immunohistochemistry [13]. Moreover, both SARS-CoV and MERS-CoV infections displayed delayed neurologic consequences, such as myopathy, Guillain-Barre syndrome peripheral neuropathy, and Bickerstaff brainstem encephalitis that occurred weeks after respiratory symptoms

[14–22]. Here, we reviewed available literature and case reports to evidence CNS involvement in COVID-19, and to identify regions of the brain that are possibly affected by SARS-CoV-2.

2. Clinical cases with central nervous system involvement

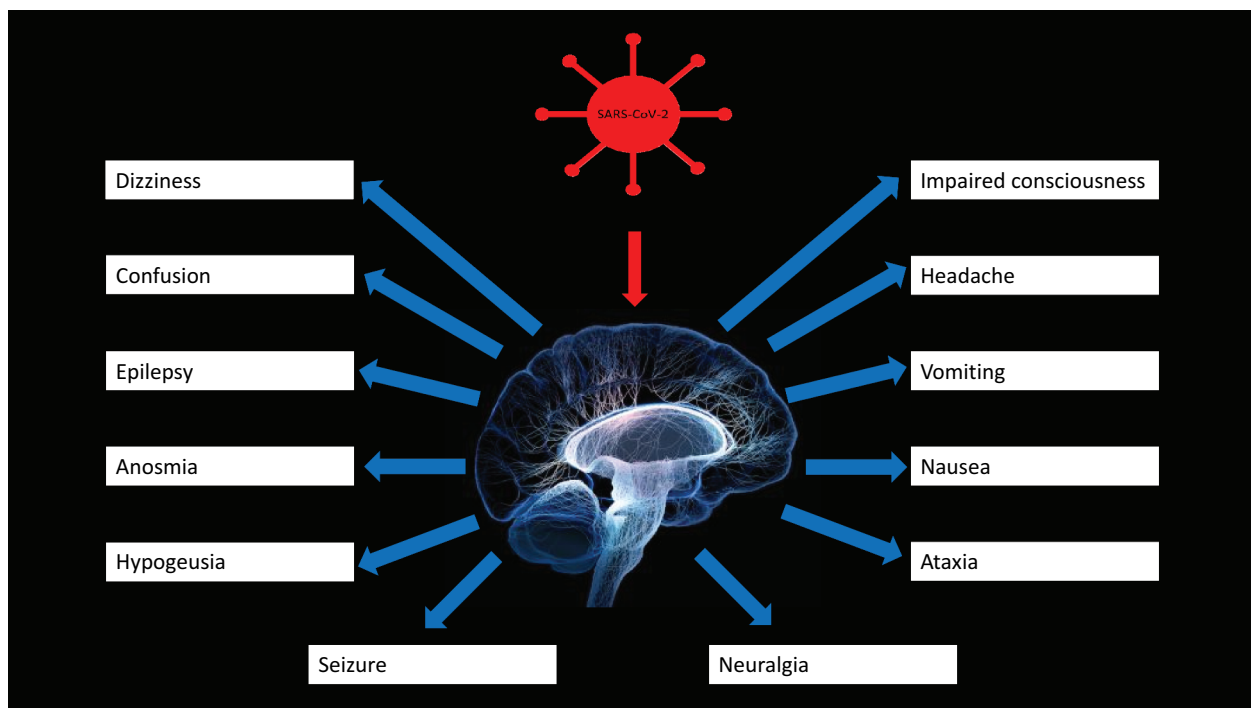
As shown in Table 1, neurological involvement has been observed among several cases of SARS-CoV-2. For example, a 30-year-old female experiencing seizures, fever, fatigue, and confusion was tested positive for SARS-CoV-2, albeit she had no history of alcohol/drug abuse, or epilepsy [18]. In another study, a female in her late 50s was diagnosed with SARS-CoV-2 infection, with cough, fever, and altered mental condition, and the final diagnosis was acute necrotizing encephalopathy associated with SARS-CoV-2 infection [21]. A 24 years old COVID-19 male patient in Japan was diagnosed with fever and meningeal irritation, while a 56 years old male patient in China was reported with encephalitis and SARS-CoV-2 in the cerebrospinal fluid (CSF) [22–24]. In addition, RNA of SARS-CoV-2 was identified in the brain samples of patients through RT-PCR [25]. Consistent with other viral/bacterial pathogens invading the CNS, infection with SARS-CoV-2 is shown to produce inflammation of the brain and spinal cord, resulting in headaches, fevers, febrile seizures, loss of consciousness, convulsions, and status epilepticus, and may trigger the onset of multiple sclerosis [26,27]. Retrospective studies of 214 COVID-19 patients revealed that patients exhibited symptoms (Figure 1) such as dizziness (17%), confusion (9%),

CONTACT Naveed Ahmed Khan  naveed5438@gmail.com  Department of Clinical Sciences, College of Medicine, University of Sharjah, University City, Sharjah, United Arab Emirates

^{*}Both authors contributed equally

Table 1. Case reports indicating SARS-CoV-2 infection of the brain. The cases are described, and gender, age, and symptoms are noted.

Case description	Gender	Age	Symptoms	Symptoms relating to CNS	References
Patient was transported to hospital after being found unconscious. SARS-CoV-2 was not detected in the nasopharyngeal but was detected in cerebrospinal fluid.	Male	24	Headache, fatigue, fever, sore throat, vomiting, loss of consciousness, seizures.	Headache, loss of consciousness, seizures	[17]
Previously healthy with no history of alcohol or drug abuse, the patient has no history of epilepsy. After experiencing seizures, patient was admitted and tested positive for SARS-CoV-2.	Female	30	Fever, fatigue, seizure, confusion.	Seizure, confusion	[18]
Patient showed no fever, runny nose or cough. Patient was diagnosed with SARS-CoV-2 infection and negative for common influenza virus. The final diagnosis was COVID-19 pneumonia complicated with Bell's palsy.	Female	65	Facial drooping, pain in the mastoid region.	Left facial paralysis.	[19]
Patient was diagnosed with SARS-CoV-2 infection. Patient did not show evidence of tuberculous or bacterial infection of the CNS. Final diagnosis was encephalitis associated with SARS-CoV-2 infection.	Male	Not noted	Fever, shortness of breath, myalgia, confusion, meningeal irritation signs (nuchal rigidity, Brudzinski sign and Kernig sign)	Confusion, meningeal irritation signs (nuchal rigidity, Brudzinski sign and Kernig sign)	[20]
Patient was diagnosed with SARS-CoV-2 infection. Tests for bacteria, herpes simplex virus, West Nile virus and varicella zoster virus were negative. Final diagnosis was acute necrotizing encephalopathy associated with SARS-CoV-2 infection.	Female	Late 50	Cough, fever, altered mental condition	Altered mental condition	[21]
SARS-CoV-2 was detected in the cerebrospinal fluid of patient. Patient was diagnosed with viral encephalitis	Not noted	56	Not noted	Not noted	[22]

**Figure 1.** The various symptoms displayed by patients that are infected with SARS-CoV-2 that can be linked to the CNS.

impaired consciousness (8%), hypogeusia (6%), anosmia (6%), acute cerebrovascular diseases (3%) (80% ischemic stroke and 20% cerebral hemorrhage), epilepsy (1%), ataxia (1%), and neuralgia [28,29], further confirming the involvement of CNS, although some symptoms, such as dizziness, might be a secondary effect of inflammation or fever. Hypogeusia and

anosmia are controlled by the parietal lobe in the brain and dizziness is linked to the parietal cortex [30,31], which suggests that the parietal lobe might be affected by SARS-CoV-2 since the abnormalities were reported in the parietal lobes of COVID-19 patients [32,33]. Four scenarios have been proposed for development of anosmia in SARS-CoV-2 patients, namely nasal obstruction and rhinorrhea, damage of support cells in

Table 2. Percentage of patients (out of 214) displaying neurological symptoms [29].

Symptoms	Percentage of cases that show symptoms		
	Severe cases	Non-severe cases	Total cases
Dizziness	19.3	15.1	16.8
Headache	17	10.3	13.1
Impaired consciousness	14.8	2.4	7.5
Acute cerebrovascular disease	5.7	0.8	2.8
Ataxia	1.1	0	0.5
Seizure	1.1	0	0.5
Hypogeusia	3.4	7.1	5.6
Hyposmia	3.4	6.3	5.1
Vision impairment	2.3	0.8	1.4
Neuralgia	4.5	0.8	2.3

the olfactory epithelium, brain infiltration affecting olfactory centers, and loss of olfactory receptor neurons [34]. In addition, ataxia that has been reported as a symptom of SARS-CoV-2 infection is linked to damaged cerebellum [35], indicating that the virus may target the cerebellum of infected individuals. Also, RNA of SARS-CoV-2 has been detected in cerebellar tissue, further enhancing the probability of the cerebellum as a target of SARS-CoV-2 [36]. However, studies need to be done to determine if this is the case. Moreover, while other signs, including headache (8%), vomiting (1%), and nausea have been found in patients with SARS-CoV-2, these effects might be secondary effects caused by inflammation or fever. Among patients with severe COVID-19, 88% of patients exhibited impaired consciousness and acute cerebrovascular diseases [37]. It has been shown that patients with cardiovascular diseases have an increased risk of neurological symptoms [38]. Encephalopathy or constant change in consciousness was described in approximately one-fifth of patients succumbing to the disease [14,39]. Several Guillain-Barre syndrome cases related to SARS-CoV-2 infection have also been reported [38]. Although neurological manifestations are mostly seen in severe cases of COVID-19, it was shown that CNS involvement of SARS-CoV-2 infection can be observed in non-severe cases (Table 2) [29]. Moreover, some of the patients were classified as ‘asymptomatic’ who suffered from hypogeusia and anosmia, while neurological deficits were identified in symptomatic patients [28]. Notably, coronaviruses can disrupt the ciliary nasal epithelium which may lead to olfactory dysfunction affecting smell sensation, and it can disrupt the cranial nerves which may lead to chemosensory dysfunction affecting taste sensation [14,40,41]. Loss of smell and taste was described in 68% and 71% of 59 SARS-CoV-2 positive patients [42]. The invasion of the medullary structures involved in respiration by SARS-CoV-2 may be linked to the respiratory failures reported in cases of COVID-19 [13,31]. Moreover, infection of the CNS by coronaviruses might lead to the creation of an inflammatory milieu that may promote the host antibodies or lymphocytes which are cross-reactive both with viral antigen and self-antigen [14,43,44]. Hence, it is of utmost importance to confirm whether patients are suffering from SARS-CoV-2 infection with neurological involvement. Moreover, SARS-CoV-2 may be latent in the CNS. Thus, there is a possibility that ‘cured’ patients might suffer from neurological diseases at a later point in time; however, there are no

experimental data to support this at present, and this needs to be investigated further [22].

3. Invasion of SARS-CoV-2 into the brain

At the molecular level, the presence of angiotensin-converting enzyme II (ACE2), a receptor that is essential for the cell entry of SARS-CoV-2, in the brain, indicates that the brain may be a potential target of the virus. But how does a respiratory virus invade the CNS? Among possible routes of entry into the CNS, the virus may enter the olfactory nerves *via* ACE2 and migrate along the neuroepithelial route to reach the brain (as evident by loss of smell in COVID-19 patients) or *via* the blood-brain barrier by binding to the ACE2 on the endothelial cells and traversing the highly selective barrier. For the latter, SARS-CoV-2 infection is associated commonly with high fever that can cause cytokine storms leading to increased permeability of the blood-brain barrier [21,26], which in turn, can provide viral access to the CNS (Figure 2). Moreover, SARS-CoV-2 invasion of sensorial receptors located in lung and airways may serve as another route for transsynaptic propagation [38].

Previous studies on SARS-CoV, another member of the coronavirus family, revealed that it can gain entry into the brain intranasally through the olfactory nerves in a transgenic mouse model expressing human ACE2 [45]. The olfactory system was analyzed for expression of ACE2, TMRPSS2 and other genes implicated in coronavirus entry and, in a mice model, it was revealed that non-neuronal cells in the olfactory epithelium and olfactory bulb, including perivascular, support and stem cells, express CoV-2 entry-associated transcripts and their associated proteins [46]. Also, it has been reported that primary olfactory sensory neurons of humans are highly susceptible to SARS-CoV-2 infection and the fact that olfactory epithelial cells have high ACE2 and TMPRSS2 expression, clinical studies identified SARS-CoV-2 infection in the olfactory nerve system and, in animal models, brain infection through intranasal delivery of SARS-CoV-2 has been demonstrated, further supports the hypothesis of olfactory route for brain infection with SARS-CoV-2 [47]. Moreover, the central glial substance (gray matter bordering the central canal that transports CSF and transfers nutrients to the spinal cord) and the choroid plexus (the site where the blood-CSF barrier is located and CSF is produced) in the human brain were found to highly express ACE2 [48–52]. Furthermore, endothelial cells and pericytes (linked to the integrity of the blood-brain barrier and part of the building blocks of neurovascular unit) exhibit high expression of ACE2 [48,53,54]. Hence, pericytes and endothelial cells may facilitate the entry of SARS-CoV-2 into the brain through the blood-brain barrier and the infection of neurovascular units. It has been suggested that movement of the blood in the cerebral circulation might favor interactions between SARS-CoV-2 that might pass into the cerebral circulation from the general circulation, and ACE2 expressed in capillary endothelium [55].

Peripheral myeloid cells that can persistently remain infected by coronaviruses may transmigrate to the CNS if

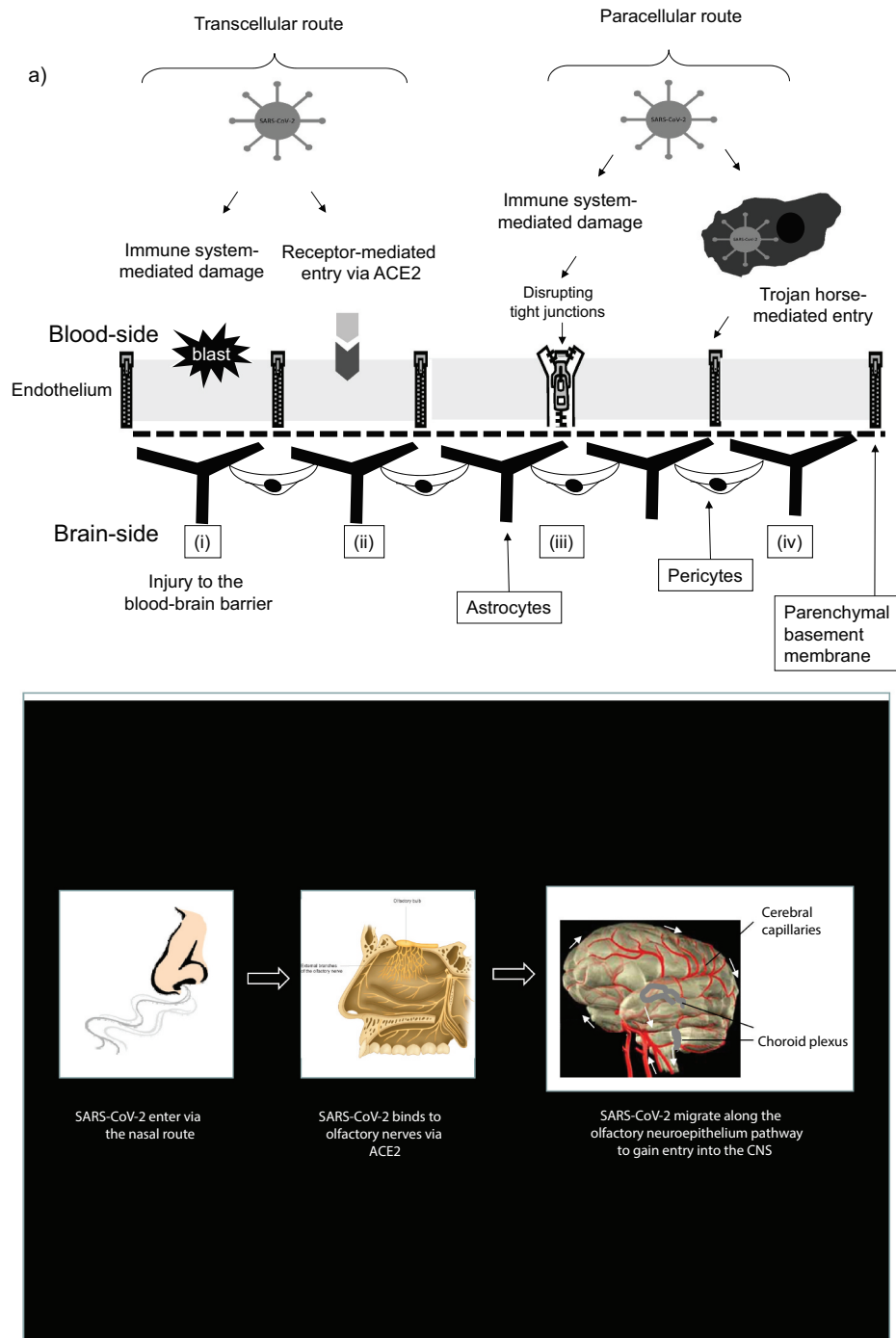


Figure 2. (A) Schematic illustration of the blood-brain barrier at the cerebral capillary endothelium. The endothelial cells are surrounded by basement membrane composed of collagen type IV, laminin, fibronectins, and heparan sulfate proteoglycans which is ensheathed by astrocytes. The endothelial cells from brain capillaries are distinct from the endothelial cells from peripheral capillaries in the presence of tight junctions, increased mitochondria, and association with astrocytes. Possible routes of SARS-CoV-2 transmigration of the endothelium at the blood-brain barrier, *via* transcellular route or paracellular route. (i) viral traversal of the blood-brain barrier by producing immune-mediated endothelial cell damage, (ii) viral traversal of the blood-brain barrier while maintaining the integrity of the endothelial cell function through receptor–ligand interactions, (iii) viral traversal of the blood-brain barrier *via* paracellular route through immune-mediated disruption of the tight junctions, and (iv) *via* infected leukocytes. **(B)** SARS-CoV-2 enters the nasal route, likely binds to the olfactory nerves *via* ACE2 and migrates along the olfactory neuroepithelial route to invade the CNS.

the permeability of the blood-brain barrier is increased by conditions such as psychological stress and inflammation [14,56–58]. Peripheral cytokines involved in the host response against SARS-CoV-2 might trigger neuropsychiatric symptoms by causing neuroinflammatory responses and

damage blood-brain interface integrity, resulting in transmigration of peripheral immune cells into the CNS and disruption of neurotransmission [14,59]. Of note, it has been reported that SARS-CoV-2 may disrupt the blood-brain barrier and is further supported by research that showed that

viral-like particles of SARS-CoV-2 found in the endothelial cells and pericytes of brain capillaries actively overrode the blood-brain barrier [60]. Moreover, it has also been suggested that could spread into the CNS by initially infecting endothelial cells of the blood-cerebrospinal fluid barrier or through organs that are not protected by the blood-brain barrier such as choroid plexus and circumventricular cerebral organs [60]. Neuronal pathway whereby the virus invade the CNS through nerve endings has also been postulated [60].

It has been reported that coronaviruses may be able to spread through air conditioning units and it was suggested that the virus might reside inside resilient *Acanthamoeba castellanii* that may boost the transmission of the virus to the CNS, as these protists have the ability to cause infection in CNS, and can act as a carrier of viruses, being well recognized as the 'Trojan horse of the microbial world' [61]. Other 'trojan horses,' such as bloodstream leukocytes, dendritic cells, and myeloid cells have been suggested, where the cells are used to gain entry into the CNS and are used as reservoirs which can be a source of virus for 'future' infections [60].

4. ACE2 in the brain

coronaviruses is determined by the Spike (S) protein of the virus since it mediates the cell fusion and receptor binding [62]. The receptor-binding domain of SARS-CoV-2 has a high affinity to human ACE2 [63]. The previous study showed that SARS-CoV-2 was able to gain entry into HeLa cells expressing human ACE2, but not the cells that did not express human ACE2, further confirming that ACE2 is an essential cell receptor used by SARS-CoV-2 [64]. Moreover, biophysical and structural analysis of SARS-CoV-2 revealed the strong affinity of the virus to ACE2 [65,66].

It has been reported that in specific areas of the human brain, including substantia nigra and brain ventricles, as well as both excitatory and inhibitory neurons in the middle temporal gyrus and posterior cingulate cortex, the expression of ACE2 is high [48]. ACE2 is high in brain nuclei of various important cells, such as neural cell bodies of different neuromodulators, including dopaminergic nuclei, serotonergic nuclei, histaminergic nuclei, and norepinephrinergic nuclei [48]. The posterior hypothalamic area (responsible for cardiovascular regulation, expression of defensive behavior and sleep-wake cycle), paraventricular nuclei of thalamus (responsible for feeding, wakefulness, appetitive motivation, regulation of stress, negative emotional behavior, and control of drug addiction), lateral hypothalamic area (responsible for control of thirst, hunger, and autonomic nervous system), and the paraventricular nuclei of hypothalamus have also been shown to highly express ACE2 [23,48,67–69]. Piriform cortex (associated with the sense of smell), amygdalo-hippocampal transition area (linked to fear manifestation), fastigial nucleus (associated with eye and body movements), and hippocampal CA2 field (linked to memory and learning) are other locations in the brain that highly express ACE2 [48,70–73]. ACE2 was also detected in excitatory neurons (linked

to emotion and memory) in the parahippocampal cortex and hippocampal formation and inhibitory neurons (vital for normal brain function) [48,74,75].

5. Significance and impact

The pandemic associated with SARS-CoV-2 continues to spread worldwide and the most favorable epidemic control scenario is the development and distribution of an effective and safe vaccine. However, considering that SARS-CoV-2 may penetrate the brain and that the human brain is immune privileged [76], it is unclear whether vaccines may be able to protect the brain from infection and/or eradicate infection of SARS-CoV-2. Furthermore, it has been reported that vaccines may trigger neurological diseases [77] and it is not known if this could further worsen the conditions of patients that are suffering from neurological manifestations due to SARS-CoV-2 infections. In addition, considering that SARS-COV-2 can traverse into the brain, drugs that are used for the treatment of COVID-19 have to be reviewed, to ensure that these drugs have good CNS penetration and ability to penetrate the blood-brain barrier [78]. The treatment and eradication of SARS-CoV-2 from the brain might also be hindered by its suggested ability to use cells such as amoebae as 'trojan horse,' since amoebae, especially cysts, are known to be very resilient [61]. The survivability of SARS-CoV-2 in free-living amoebae warrants further studies since studies will reveal if the amoebae has a role as facilitators for the transmission of the virus and/or protection of the virus during treatment which might be responsible for relapses.

6. Conclusion

While SARS-CoV-2 is known to affect the respiratory system, mounting evidence suggests that it invades the CNS. Several case reports have demonstrated that patients showed symptoms related to brain infection. Based on the symptoms, the parietal lobe and the cerebellum might be the likely targets of SARS-CoV-2; however, further work is needed to elucidate this. The presence of ACE2, used by SARS-CoV-2 for cell entry, in the brain as well as detection of the virus in the CSF, further assert that SARS-COV-2 targets the brain. Therefore, medical practitioners should take that into account when dealing with patients suffering from COVID-19.

Declaration of funding

No funding was received to produce this article

Declaration of financial/other relationships

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

The authors declare that there is no conflict of interest.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors' contributions

RS and NAK envisioned the idea. MRM reviewed the available literature under the supervision of RS and NAK. MRM and RS wrote the first draft of the manuscript. NAK and RS corrected the manuscript.

Declaration of interest

No potential conflict of interest was reported by the authors.

ORCID

Ruqaiyyah Siddiqui  <http://orcid.org/0000-0001-9646-6208>

Mohammad Ridwane Mungroo  <http://orcid.org/0000-0002-8056-4011>

References

- Johns Hopkins Coronavirus Resource Center. COVID-19 map. 2020. [Online] [cited 2020 Dec 10]. Available from: <https://coronavirus.jhu.edu/map.html>
- Mungroo MR, Khan NA, Siddiqui R. Novel coronavirus: current understanding of clinical features, diagnosis, pathogenesis, and treatment options. *Pathogens*. 2020;9(4):297.
- Zumla A, Chan JF, Azhar EI, et al. Coronaviruses—drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327–347.
- Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. *Immunol Res*. 2014;59(1–3):118–128.
- Cheng VC, Lau SK, Woo PC, et al. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev*. 2007;20(4):660–694.
- Chan JF, Lau SK, To KK, et al. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clin Microbiol Rev*. 2015;28(2):465–522.
- Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367(19):1814–1820.
- Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1967–1976.
- Wu D, Wu T, Liu Q, et al. The SARS-CoV-2 outbreak: what we know. *Int J Infect Dis*. 2020;94:44–48.
- Forster P, Forster L, Renfrew C, et al. Phylogenetic network analysis of SARS-CoV-2 genomes. *PNAS*. 2020;117(17):9241–9243.
- Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 2005;202(3):415–424.
- Li K, Wohlford-Lenane C, Perlman S, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis*. 2016;213(5):712–722.
- Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol*. 2007;170(4):1136–1147.
- Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. 2020;87:34–39.
- Tsai LK, Hsieh ST, Chao CC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol*. 2004;61(11):1669–1673.
- Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol*. 2017;13(3):227–233.
- Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55–58.
- Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: a case report. *Iran Red Crescent Med J*. 2020;22(3):e102828.
- Wan Y, Cao S, Fang Q, et al. Coronavirus disease 2019 complicated with Bell's palsy: a case report. *Res Square*. 2020. doi:10.21203/rs.3.rs-23216/v1
- Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun*. 2020;88:945–946.
- Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. 2020;296(2):201187.
- Zhou L, Zhang M, Wang J, et al. Sars-Cov-2: underestimated damage to nervous system. *Travel Med Infect Dis*. 2020;24:101642.
- Katagiri A, Okamoto K, Thompson R, et al. Posterior hypothalamic modulation of light-evoked trigeminal neural activity and lacrimation. *Neuroscience*. 2013;246:133–141.
- Li YC, Bai WZ, Hashikawa T. Response to Commentary on “The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients”. *J Med Virol*. 2020;92(7):707–709.
- Rommelink M, De Mendonça R, D'Haene N, et al. Unspecific post-mortem findings despite multiorgan 1 viral spread in COVID-19 patients. *Crit Care*. 2020;24(495):1–10.
- Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther*. 2020;26(5):499.
- Li H, Xue Q, Xu X. Involvement of the nervous system in SARS-CoV-2. *Infect Neurotox Res*. 2020;38(1):1–7.
- Shaikh AG, Mitoma H, Manto M. Cerebellar scholars' challenging time in COVID-19 pandemia. *Cerebellum*. 2020;19(3):343–344.
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683–690.
- Brain & Spine Foundation. Anatomy of the brain and spine. 2020 [Online] [cited 2020 Dec 20]. Available from: <https://www.brainandspine.org.uk/information-and-support/anatomy-of-the-brain-and-spine/>
- Johns Hopkins Medicine. Where does dizziness come from? 2020. [Online] [cited 2020 Dec 15]. Available from: https://www.hopkinsmedicine.org/news/media/releases/where_does_dizziness_come_from
- Katal S, Balakrishnan S, Gholamrezanezhad A. Neuroimaging findings in COVID-19 and other coronavirus infections: a systematic review in 116 patients. *J Neuroradiol*. 2020. DOI:10.1016/j.neurad.2020.06.007
- Bougakov D, Podell K, Goldberg E. Multiple neuroinvasive pathways in COVID-19. *Mol Neurobiol*. 2020;1–12. DOI:10.1007/s12035-020-02152-5
- Butowt R, von Bartheld CS. Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. *Neuroscientist*. 2020;107385842095690. DOI:10.1177/1073858420956905
- National Ataxia Foundation. What is ataxia? - National ataxia foundation. 2020. [Online] [cited 2020 Dec 16]. Available from: <https://ataxia.org/what-is-ataxia/>
- Freij BJ, Gebara BM, Tariq R, et al. Fatal central nervous system co-infection with SARS-CoV-2 and tuberculosis in a healthy child. *BMC Pediatr*. 2020;20(1):1–7.
- Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552–555.
- Tsatsakis A, Calina D, Falzone L, et al. SARS-CoV-2 pathophysiology and its clinical implications: an integrative overview of the pharmacotherapeutic management of COVID-19. *Food Chem Toxicol*. 2020;146:111769.
- Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:1295.
- Chilvers MA, McKean M, Rutman A, et al. The effects of coronavirus on human nasal ciliated respiratory epithelium. *Eur Respir J*. 2001;18(6):965–970.
- Bromley SM. Neurolocalization of taste disorders. *Handb Clin Neurol*. 2019;164(2019):303–323.

42. Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol.* 2020;10(7):806–813.
43. Fairweather D, Frisancho-Kiss S, Rose NR. Viruses as adjuvants for autoimmunity: evidence from Coxsackievirus-induced myocarditis. *Rev Med Virol.* 2005;15(1):17–27.
44. Rose NR. Negative selection, epitope mimicry and autoimmunity. *Curr Opin Immunol.* 2017;49:51–55.
45. Netland J, Meyerholz DK, Moore S, et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* 2008;82(15):7264–7275.
46. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv.* 2020;6(31):eabc5801.
47. Bodnar B, Patel K, Ho W, et al. Cellular mechanisms underlying neurological/neuropsychiatric manifestations of COVID-19. *J Med Virol.* 2020;1–16. DOI:10.1002/jmv.26720
48. Chen R, Yu J, Wang K, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *BioRxiv.* 2020. DOI:10.1101/2020.04.07.030650
49. Thouvenin O, Keiser L, Cantaut-Belarif Y, et al. Origin and role of the cerebrospinal fluid bidirectional flow in the central canal. *Elife.* 2020;9:e47699.
50. Lun MP, Monuki ES, Lehtinen MK. Development and functions of the choroid plexus–cerebrospinal fluid system. *Nat Rev Neurosci.* 2015;16(8):445–457.
51. Ghersi-Egea JF, Strazielle N, Catala M, et al. Molecular anatomy and functions of the choroidal blood–cerebrospinal fluid barrier in health and disease. *Acta Neuropathol.* 2018;135(3):337–361.
52. Valente LA, Begg LR, Filiano AJ. Updating neuroimmune targets in central nervous system dysfunction. *Trends Pharmacol Sci.* 2019;40(7):482–494.
53. Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat Neurosci.* 2016;19(6):771–783.
54. Daneman R, Zhou L, Kebede AA, et al. Pericytes are required for blood–brain barrier integrity during embryogenesis. *Nature.* 2010;468(7323):562–566.
55. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* 2020;11(7):995–998.
56. Arbour N, Day R, Newcombe J, et al. Neuroinvasion by human respiratory coronaviruses. *J Virol.* 2000;74(19):8913–8921.
57. Desforges M, Le Coupance A, Dubeau P, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses.* 2020;12(1):14.
58. Desforges M, Miletti TC, Gagnon M, et al. Activation of human monocytes after infection by human coronavirus 229E. *Virus Res.* 2007;130(1–2):228–240.
59. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiol Rev.* 2018;98(1):477–504.
60. Lima M, Siokas V, Aloizou AM, et al. Unraveling the possible routes of SARS-COV-2 invasion into the central nervous system. *Curr Treat Options Neurol.* 2020;22(11):1–5.
61. Siddiqui R, Khan NA. War on terror cells: strategies to eradicate “novel coronavirus” effectively. *ACS Chem Neurosci.* 2020;11(9):1198–1199.
62. He Y, Zhou Y, Liu S, et al. Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: implication for developing subunit vaccine. *Biochem Biophys Res Commun.* 2004;324(2):773–781.
63. Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol.* 2020;94(7):e00127–20.
64. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270–273.
65. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020;367(6483):1260–1263.
66. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature.* 2020;581(7807):215–220.
67. Chen B, Xu C, Wang Y, et al. A disinhibitory nigra-parafascicular pathway amplifies seizure in temporal lobe epilepsy. *Nat Commun.* 2020;11(1):1–6.
68. Ren S, Wang Y, Yue F, et al. The paraventricular thalamus is a critical thalamic area for wakefulness. *Science.* 2018;362(6413):429–434.
69. Stuber GD, Wise RA. Lateral hypothalamic circuits for feeding and reward. *Nat Neurosci.* 2016;19(2):198–205.
70. Cheng H, Wang Y, Chen J, et al. The piriform cortex in epilepsy: what we learn from the kindling model. *Exp Neurol.* 2020;324:113137.
71. Fujisaki M, Hashimoto K, Iyo M, et al. Role of the amygdalo-hippocampal transition area in the fear expression: evaluation by behavior and immediate early gene expression. *Neuroscience.* 2004;124(1):247–260.
72. Zhang XY, Wang JJ, Zhu JN. Cerebellar fastigial nucleus: from anatomic construction to physiological functions. *Cerebellum Ataxias.* 2016;3(1):9.
73. Dudek SM, Alexander GM, Farris S. Rediscovering area CA2: unique properties and functions. *Nat Rev Neurosci.* 2016;17(2):89.
74. Cardin JA. Inhibitory interneurons regulate temporal precision and correlations in cortical circuits. *Trends Neurosci.* 2018;41(10):689–700.
75. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain.* 2014;137(1):12–32.
76. Calina D, Hartung T, Docea AO, et al. COVID-19 vaccines: ethical framework concerning human challenge studies. *DARU J Pharm Sci.* 2020;28:807–812.
77. Kostoff RN, Kanduc D, Porter AL, et al. Vaccine- and natural infection-induced mechanisms that could modulate vaccine safety. *Toxicol Rep.* 2020;7:1448–1458.
78. Danta CC. CNS penetration ability: a critical factor for drugs in the treatment of SARS-CoV-2 brain infection. *ACS Chem Neurosci.* 2020;11(15):2137–2144.