


Review

Emerging neurotropic features of SARS-CoV-2

Wen-Rong Zhan, Jing Huang, Peng-Ming Zeng, Wei-Ya Tian, and Zhen-Ge Luo  *

School of Life Science and Technology, ShanghaiTech University, Shanghai 201210, China

* Correspondence to: Zhen-Ge Luo, E-mail: luozhg@shanghaitech.edu.cn

Edited by Jiarui Wu

The prevailing coronavirus disease-19 (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has presented some neurological manifestations including hyposmia, hypogeusia, headache, stroke, encephalitis, Guillain–Barre syndrome, and some neuropsychiatric disorders. Although several cell types in the brain express angiotensin-converting enzyme-2 (ACE2), the main SARS-CoV-2 receptor, and other related proteins, it remains unclear whether the observed neurological manifestations are attributed to virus invasion into the brain or just comorbidities caused by dysregulation of systemic factors. Here, we briefly review the neurological manifestations of SARS-CoV-2, summarize recent evidence for the potential neurotropism of SARS-CoV-2, and discuss the potential mechanisms of COVID-19-associated neurological diseases.

Keywords: SARS-CoV-2, ACE2, brain invasion, neurological manifestations

Introduction

In less than two decades, three coronavirus outbreaks prevailed to form major epidemics that mainly attack the respiratory system of patients, including severe acute respiratory syndrome (SARS) caused by SARS-coronavirus (SARS-CoV) in 2002–2003, Middle East respiratory syndrome (MERS) by MERS-CoV in 2012, and the ongoing coronavirus disease-19 (COVID-19). SARS affected a total of 8096 people and caused ~9.56% of deaths (De Wit et al., 2016), and MERS was responsible for 34.4% of deaths in 2494 total patients (Berger, 2020). As of May 10, 2021, COVID-19 has caused nearly 160 million cases and over 3.3 million deaths globally and it is becoming the most severe pandemic over the last century.

The most common symptoms of COVID-19 are fever, cough, fatigue, muscle pain, and shortness of breath (Garg et al., 2020; Grasselli et al., 2020; Guan et al., 2020; Huang et al., 2020a). Some reports showed that >36.4% of confirmed cases presented neurological manifestations, including dizziness, headache, hypogeusia, and hyposmia (Helms et al., 2020; Mao et al., 2020). Cerebrovascular diseases such as stroke have also been identified in some patients (Giustozzi et al., 2020; Oxley et al., 2020; Viguier et al., 2020). The neurological involvement is not specific for COVID-19, because

similar neurological abnormalities are also observed following infections from other coronaviruses, such as SARS-CoV and MERS-CoV (Glass et al., 2004; Li et al., 2016; Ellul et al., 2020).

Like SARS-CoV, SARS-CoV-2 also uses protease-processed spike (S) protein to invade host cells through angiotensin-converting enzyme-2 (ACE2) (Li et al., 2003; Hoffmann et al., 2020; Walls et al., 2020). The cellular serine proteases transmembrane protease serine 2 (TMPRSS2) and furin are responsible for S protein priming and pre-activated cleavage, respectively, to facilitate the access to host cells (Hoffmann et al., 2020; Shang et al., 2020). In addition, other cellular receptors, such as Neuropilin-1 (NRP-1) and CD147, may mediate the virus entry into the host cell through ACE2-independent manner (Cantuti-Castelvetri et al., 2020; Daly et al., 2020; Zhou et al., 2020). Using pseudovirus system, it has been shown that SARS-CoV-2 entry and replication can be facilitated by the proprotein convertase furin, the cell surface protease TMPRSS2, and the lysosomal proteases cathepsins (Shang et al., 2020). The presence of a polybasic furin-type cleavage site in the SARS-CoV-2 S protein might explain why SARS-CoV-2 spreads much more rapidly than SARS-CoV (Coutard et al., 2020).

ACE2 protein was found to be expressed in neurons of the brain (Song et al., 2021), and NRP-1 expression was observed in the olfactory system (Kawakami et al., 1996), including neurons of the olfactory epithelium (Cantuti-Castelvetri et al., 2020). The expression of putative SARS-CoV-2 receptors in several neuronal cell types raised possibility of direct invasion of SARS-CoV-2 into the brain (Yang et al., 2020).

Received September 12, 2020. Revised May 6, 2021. Accepted May 12, 2021.
© The Author(s) (2021). Published by Oxford University Press on behalf of *Journal of Molecular Cell Biology*, CEMCS, CAS.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Table 1 Neurological and neuropsychiatric features of COVID-19 patients.

Neurological symptoms	Etiology/pathophysiology	References
Cerebrovascular disease		
Ischemic strokes	Neuroimaging, viral presence in CSF, inflammatory factors	Poyiadji et al. (2020); Mao et al. (2020); Pleasure et al. (2020); Jin et al. (2020); Ellul et al. (2020)
Brain hemorrhage		
Thrombocytopenia		
CNS neurological disease		
Encephalopathy	Neuroimaging, viral presence in CSF, CNS infection, spine imaging	Helms et al. (2020); Poyiadji et al. (2020); Mao et al. (2020); Duong et al. (2020); Asadi-Pooya and Simani (2020)
Encephalitis		
Myelitis		
PNS neurological disease		
Guillain–Barre	PNS infection, nerve demyelination, neuromuscular junction, immune dysregulation	Sedaghat and Karimi (2020); (Zhao et al., 2020a)
Myalgia		
Paralysis		
Sensory impairment		
Hyposmia	Olfactory viral invasion, CNS autoimmunity	Poyiadji et al. (2020); Najjar et al. (2020); Mao et al. (2020); Sohal and Mansur (2020)
Hyposmia		
Anosmia		
Ageusia		
Seizure	Neuroimaging, viral presence in CSF	Mao et al. (2020); Poyiadji et al. (2020); Duong et al. (2020); Sohal and Mansur (2020)
Neuropsychiatric disorder		
Depression	Not reported	Mao et al. (2020); Rogers et al. (2020); Varatharaj et al. (2020)
Anxiety		
Confusion		
Agitation		
Delirium		

COVID-19-associated neurological manifestations

Accumulating case reports have shown that COVID-19 patients exhibit a wide range of neurological manifestations of either the central nervous system (CNS) or the peripheral nervous system (PNS), in isolation or together with other features (Ellul et al., 2020; Iadecola et al., 2020; Table 1). For example, a retrospective study from Wuhan, China, reported that 53 of 214 COVID-19 patients (~25%) had CNS symptoms, including 28 with headache, 36 with dizziness, and 16 with consciousness impairment (Mao et al., 2020). Notably, only ~50% of those with CNS symptoms (27/53) showed severe respiratory problem. In another study carried out in France for 58 COVID-19 patients, 49 (84%) had neurological complications, including 40 with encephalopathy (Helms et al., 2020), which was defined based on alterations in mental status, such as confusion, agitation, disorientation, or delirium. The alterations in mental status were most likely caused by systemic disorder, rather than encephalitis resulted from direct SARS-CoV-2 infection, because only a few cases showed modest amount of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) (Huang et al., 2020b; Moriguchi et al., 2020).

In addition to encephalopathy, cerebrovascular manifestations are also seen in some of COVID-19 patients. Ischemic stroke has been reported in 1%–6% COVID-19 patients (Klok et al., 2020; Mao et al., 2020; Merkler et al., 2020; Yaghi et al., 2020), and notably, the rates are several folds higher than that in patients with common influenza (Merkler et al., 2020). The COVID-19-associated endothelial dysfunction might be related with increased susceptibility to cerebrovascular disease (Klok et al., 2020).

Compared to influenza patients, much higher ratio of COVID-19 patients reported olfactory dysfunction or gustatory disorders (Ellul et al., 2020). In a multicenter European study of 417 COVID-19 patients, 85.6% reported decreased sense of smell, and 79.6% reported a complete loss of taste (Lechien et al., 2020). Although anosmia and ageusia are emerging as common symptoms of COVID-19, it remains unclear whether these abnormalities were caused by direct invasion of olfactory nerve or just because of *co-ryza*, which can occur in many other respiratory viral infections.

Systemic inflammation and dysregulated immune responses elicited after acute phase of viral infection are known to cause CNS or PNS neurological complications. Up to now, only rare cases of post-infectious CNS inflammations, typically encephalomyelitis and myelitis, were reported (Zanin et al., 2020; Zhao et al., 2020b; Zhang et al., 2021). More cases of Guillain–Barre syndrome resulted from immune attack on PNS were reported in COVID-19 patients, with evidence of axonal demyelination and consequent symptoms of muscle weakness, ataxia, or areflexia (Dinkin et al., 2020; Gutiérrez-Ortiz et al., 2020; Marta-Enguita et al., 2020; Toscano et al., 2020). Interestingly, a recent study showed that all the brain regions with SARS-CoV-2 signals had minimal lymphocyte or leukocyte infiltration, suggesting that SARS-CoV-2 may not elicit strong post-infectious immune response (Song et al., 2021). This feature is distinct from other neurotropic viruses like ZIKV, rabies virus, and herpes virus. In line with this notion, SARS-CoV-2-infected brain organoids exhibited little change in the pathways related with defense response to virus, cellular response to type I interferon, and innate immune response, which were observed in ZIKV-infected organoids (Song et al., 2021).

Neurotropic characteristics of SARS-CoV-2

Of the seven types of coronaviruses that infect humans, at least two strains have been shown to be able to enter and persist in the brain, including SARS-CoV (Arbour et al., 2000; Gu et al., 2005). The high similarity of SARS-CoV-2 in its nucleotide sequence to SARS-CoV, in particular the receptor-binding domain, indicates that it may also invade the host cells through ACE2 (Lu et al., 2020; Wang et al., 2020a). In support of this conclusion, intranasal infection of mice expressing human ACE2 with SARS-CoV-2 caused high viral loads in the lung, trachea, and brain (Sun et al., 2020).

In line with frequently observed loss of smell in COVID-19 patients, ACE2 and TMPRSS2 that mediates proteolytic processing of the S protein were observed in the olfactory epithelium, but not olfactory neurons, in both murine and human samples (Bilinska et al., 2020; Brann et al., 2020). Varied expression of ACE2 was observed in human neurons in a subtype- and region-specific manner, and high expression of ACE2 and TMPRSS2 was observed in pericytes, endothelial cells, or choroid plexus cells (He et al., 2020; Jacob et al., 2020; Ramani et al., 2020; Chen et al., 2021; Song et al., 2021).

Other evidence supporting the neurotropism of SARS-CoV-2 came from *in vitro* cellular or organoid models. In a cultured human brain organoid model, SARS-CoV-2 exhibited neuroinvasive ability in an ACE2-dependent manner, leading to neuronal death (Song et al., 2021). Several independent studies using brain organoids have also shown neurotropism of SARS-CoV-2 in their brain organoid systems (Ramani et al., 2020; Yang et al., 2020; Zhang et al., 2020). However, the results for targeted cell types were inconsistent among different studies. Some studies showed that SARS-CoV-2 preferably targets mature neurons (Ramani et al., 2020; Song et al., 2021), whereas other studies state that SARS-CoV-2 cannot target neuronal cell types (Pellegrini et al., 2020) or only has minimal neuronal infection ability (Jacob et al., 2020). Interestingly, in the brain organoids of hippocampal-like regions, SARS-CoV-2 signals were found to be enriched in choroid plexus epithelia-like cells and SARS-CoV-2 entry can lead to damages for the integrity of choroid plexus epithelium (Jacob et al., 2020; Pellegrini et al., 2020), suggesting that barrier disruption might facilitate SARS-CoV-2 invasion into the brain.

It is worth noting that SARS-CoV-2-positive neurons in human brain organoids exhibit mis-localization of axonal protein Tau to the cell soma and aberrant Tau phosphorylation, a phenomenon often seen in tauopathy-related neurodegeneration diseases (Ramani et al., 2020). In accordance with positive association between the ApoE4, a strong genetic risk factor for Alzheimer disease, and severe COVID-19 (Kuo et al., 2020), the ApoE4/4 neurons, astrocytes, or brain organoids exhibit increased rate of SARS-CoV-2 infection (Wang et al., 2021). These results indicate that particular attention should be paid to the potential long-term effects of SARS-CoV-2 infection on different patient populations, in particular the neurological and neuropsychological morbidities.

In histological analyses of the deceased individuals with COVID-19, SARS-CoV-2 RNA and protein were found in epithelial tissues of the olfactory mucosa and defined CNS regions receiving olfactory neuronal projections (Meinhardt et al., 2021). Notably, the SARS-CoV-2 S protein was observed in cortical neurons of ischemic regions in brains of some cases of post-mortem COVID-19 patients, who were diagnosed with severe encephalopathy and multiple ischemic infarcts (Song et al., 2021). These studies have provided direct evidence supporting neurotropism of SARS-CoV-2 in COVID-19 patients and substantiated the findings obtained in human brain organoids.

Possible mechanisms of neurological manifestations

Viral entry to the brain via the olfactory bulb is a possible route given frequent anosmia in COVID-19 patients (Figure 1). In support of this possibility, the brain has been shown to be one of the major organs in hACE2 transgenic mice after intranasal infection with either SARS-CoV or SARS-CoV-2 (Tseng et al., 2007; Netland et al., 2008; Sun et al., 2020). Notably, magnetic resonance imaging analysis in a COVID-19 patient with anosmia showed a transient hyperintensity in the olfactory cortex, as well as a subtle hyperintensity in the olfactory bulb suggestive of viral infection (Politi et al., 2020). The presence of SARS-CoV-2 RNA and protein in the olfactory mucosa, its neuronal projections, and several CNS regions has provided direct evidence supporting the olfactory route of CNS entry by SARS-CoV-2 (Meinhardt et al., 2021). The presence of SARS-CoV-2 in defined neuroanatomical areas receiving olfactory tract projections, including the primary respiratory and cardiovascular control center, raises the possibility of axonal transport and/or trans-synaptic spread of virus (Meinhardt et al., 2021; Zubair et al., 2020). The trans-synaptic spread of virus has been demonstrated for several other types of coronaviruses, such as HCoV-OC43 (Dub  et al., 2018).

Pathogens like viruses can enter the blood and circulate to cerebrovascular after crossing the blood–brain barrier (BBB), following viremia or through infected immune cells (Bohmwald et al., 2018). Of note, remarkable percentage of the blood specimen, varying from 1% to 22%, derived from COVID-19 patients, displayed SARS-CoV-2 RNAemia suggestive of viremia (Huang et al., 2020a; Peng et al., 2020; Wang et al., 2020b). The lack of detailed clinical information of patients limits the correlation of viremia with prognosis or disease course. The BBB formed by tight junctions consisted of endothelial cells together with surrounding pericytes and astrocytes plays a crucial role in maintaining the homeostasis of the brain and prevents pathogen invasion into the brain. Virions in the blood can directly attach to endothelial and pericytes through viral entry receptors for SARS-CoV-2, leading to alterations of the tight junction. High expression of ACE2 and TMPRSS2 in pericytes and endothelial cells supports this possibility (He et al., 2020; Chen et al., 2021). The transcytosis transport across the endothelia and pericytes by endocytic vesicles is an alternative pathway, as that done by other neuroinvasive respiratory

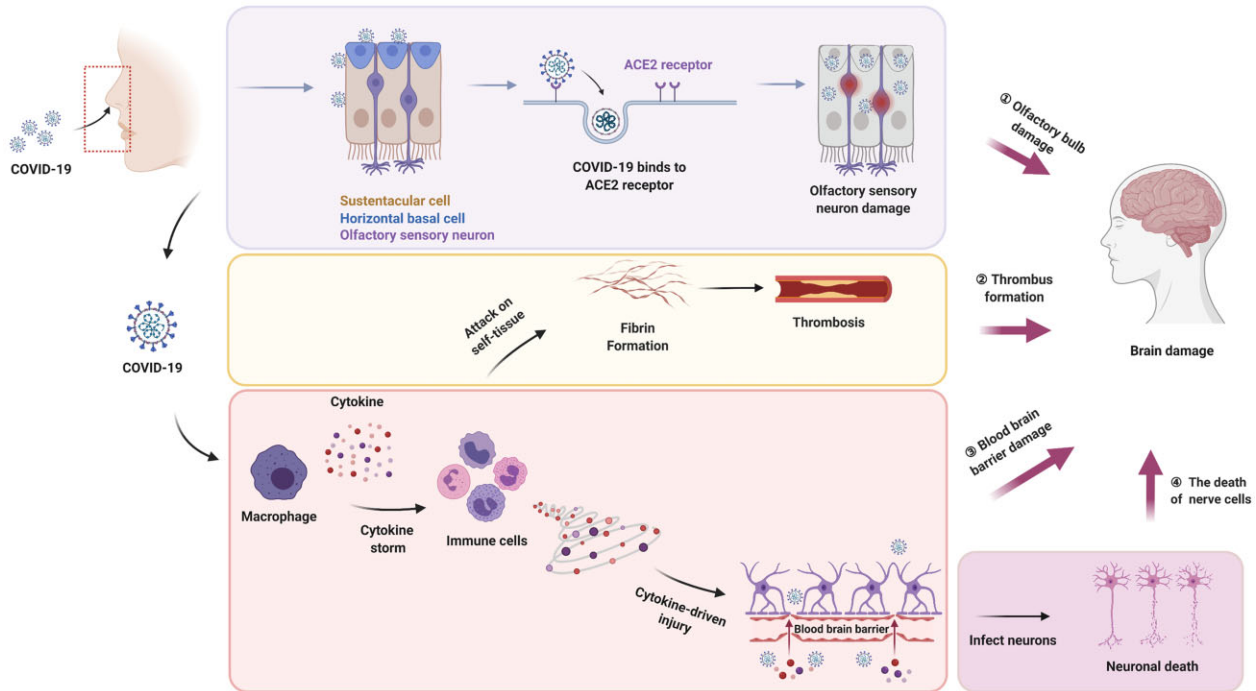


Figure 1 Possible mechanism for the effects of SARS-CoV-2 on the nervous system. SARS-CoV-2 may cause damage to the nervous system through direct or indirect pathways. The direct infection of SARS-CoV-2 into sustentacular cells and horizontal basal cells impairs the function of olfactory neurons, which leads to the loss of smell sense and may further cause brain damage. SARS-CoV-2 induces an immune response after it enters the human body. The cytokine storm formed in the process of immune response can cause thrombosis and destruction of the BBB, and thus indirectly cause brain damage. When the BBB is broken, SARS-CoV-2 may cross the barrier and directly infect nerve cells by binding to specific receptors on nerve cells.

viruses (Suen et al., 2014; Bohmwald et al., 2018). The presence of SARS-CoV-2 S protein in cerebral and leptomeningeal endothelial cells also supports the possible route of viral entry along CNS endothelia (Meinhardt et al., 2021).

Dysregulated immune response like cytokine storm is a common phenomenon in many severe COVID-19 patients (Mehta et al., 2020). High levels of inflammatory cytokines saturate in the blood can cause breakdown of the BBB (Poyiadji et al., 2020; Quirch et al., 2020), which may facilitate virion entry into the brain (Figure 1). Furthermore, cytokines may cause damage to the CNS by facilitating the formation of thrombosis, leading to cerebrovascular diseases (Hoffmann et al., 2020; Figure 1). It has been suggested that the infected immune cells can cross the BBB via the paracellular route (Suen et al., 2014; Bohmwald et al., 2018). Indeed, a report demonstrated that circulating monocytes, B lymphocytes, and CD4⁺ T lymphocytes are the main cell types frequently detected with positive signals for SARS-CoV-2 (Pontelli et al., 2020). Interestingly, immune cells with SARS-CoV-2 settled down in the lung of COVID-19 patients (Pontelli et al., 2020), implying the ‘Trojan Horse’ invasion mechanism—infected immune cell may mediate viral invasion into organs, including the brain. This entry strategy has been suggested to be used by immunodeficiency virus (HIV-1) (Albright et al., 2003; Spindler and Hsu, 2012) and

another coronavirus HCoV-229E (Desforges et al., 2007). Further studies are needed to confirm whether SARS-CoV-2 entry into the brain is also via this route.

Conclusion and perspective of future study

In addition to the potential direct cytolytic effect, SARS-CoV-2 can also lead to brain dysfunction and neuronal damage through indirect systemic effects such as secondary inflammatory response (Van den Pol, 2006). In the absence of direct viral invasion, the neurotoxicity of the cytokine storm itself may cause damage to the CNS, such as acute necrotizing encephalopathy (Ouattara et al., 2011). Besides, cytokines may also cause brain damage by activating the thrombotic pathway (Hoffmann et al., 2020), which may lead to ischemic stroke.

Although many reports demonstrated that SARS-CoV-2 could cause nervous system diseases, the underlying mechanism is not clear. The effects of SARS-CoV-2 on the CNS most likely involve the direct entry of viruses into neurons, which causes neuronal cell death, and indirect pathway through the cytokine storm and thrombosis (Figure 1). In addition, SARS-CoV-2 may invade the CNS through axonal transport and trans-synaptic transfer via the olfactory nerve and through infection of pericytes or endothelial cells that make up BBB or leukocytes that

pass through BBB (Zubair et al., 2020; Alquisiras-Burgos et al., 2021; Figure 1). These possibilities can be thoroughly verified using animal models such as hACE2 transgenic mice, which can be used to resemble the systemic effects of the disease.

Besides ACE2, other receptors and accessory proteins have been shown to facilitate SARS-CoV-2 entry into the cell. What factors mediate the interaction of SARS-CoV-2 with human brain remains to be studied systematically. Their expression and subcellular localization in human cell types, including various neurons, glia, and vascular cells, would be essential information. Furthermore, CNS control of systematic functions, such as autonomic pathways that control breathing, would help to disentangle neurological and systematic complications. Given the ongoing trends of COVID-19 pandemic, the long-term neurological and psychiatric sequelae of SARS-CoV-2 infection need serious consideration and follow-up tracking studies.

Acknowledgements

Due to the rapid progress in the field, the authors apologize for the ignorance of other relevant works.

Funding

This study was partially supported by grants from the Frontier Key Project of the Chinese Academy of Sciences (QYZDJ-SSW-SMC025), Shanghai Municipal Science and Technology Projects (2018SHZDZX05 and 201409001700), and the National Key R&D Program of China (2017YFA0700500).

Conflict of interest: none declared.

References

- Albright, A.V., Soldan, S.S., and González-Scarano, F. (2003). Pathogenesis of human immunodeficiency virus-induced neurological disease. *J. Neurovirol.* *9*, 222–227.
- Alquisiras-Burgos, I., Peralta-Arrieta, I., Alonso-Palomares, et al. (2021). Neurological complications associated with the blood–brain barrier damage induced by the inflammatory response during SARS-CoV-2 infection. *Mol. Neurobiol.* *58*, 520–535.
- Arbour, N., Day, R., Newcombe, J., et al. (2000). Neuroinvasion by human respiratory coronaviruses. *J. Virol.* *74*, 8913–8921.
- Asadi-Pooya, A.A., and Simani, L. (2020). Central nervous system manifestations of COVID-19: a systematic review. *J. Neurol. Sci.* *413*, 116832.
- Berger, J.R. (2020). COVID-19 and the nervous system. *J. Neurovirol.* *26*, 143–148.
- Bilinska, K., Jakubowska, P., Von Bartheld, C.S., et al. (2020). Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with age. *ACS Chem. Neurosci.* *11*, 1555–1562.
- Bohmwald, K., Galvez, N.M.S., Rios, M., et al. (2018). Neurologic alterations due to respiratory virus infections. *Front. Cell. Neurosci.* *12*, 386.
- Brann, D.H., Tsukahara, T., Weinreb, C., et al. (2020). Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci. Adv.* *6*, eabc5801.
- Cantuti-Castelvetri, L., Ojha, R., Pedro, L.D., et al. (2020). Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* *370*, 856–860.
- Chen, R., Wang, K., Yu, J., et al. (2021). The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front. Neurol.* *11*, 573095.
- Coutard, B., Valle, C., de Lamballerie, X., et al. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res.* *176*, 104742.
- Daly, J.L., Simonetti, B., Klein, K., et al. (2020). Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science* *370*, 861.
- Desforges, M., Milette, T.C., Gagnon, M., et al. (2007). Activation of human monocytes after infection by human coronavirus 229E. *Virus Res.* *130*, 228–240.
- De Wit, E., van Doremalen, N., Falzarano, D., et al. (2016). SARS and MERS: recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.* *14*, 523–534.
- Dinkin, M., Gao, V., Kahan, J., et al. (2020). COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* *95*, 221.
- Dubé, M., Le Coupanec, A., Wong, A.H., et al. (2018). Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J. Virol.* *92*, e00404-18.
- Duong, L., Xu, P., and Liu, A. (2020). Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain Behav. Immun.* *87*, 33.
- Ellul, M.A., Benjamin, L., Singh, B., et al. (2020). Neurological associations of COVID-19. *Lancet Neurol.* *19*, 767–783.
- Glass, W.G., Subbarao, K., Murphy, B., et al. (2004). Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J. Immunol.* *173*, 4030.
- Garg, S., Kim, L., Whitaker, M., et al. (2020). Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, March 1–30, 2020. *Morb. Mortal. Wkly. Rep.* *69*, 458–464.
- Giustozzi, M., Acciarresi, M., Agnelli, G., et al. (2020). Safety of anticoagulation in patients treated with urgent reperfusion for ischemic stroke related to atrial fibrillation. *Stroke* *51*, 2347–2354.
- Grasselli, G., Zangrillo, A., Zanella, A., et al. (2020). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* *323*, 1574–1581.
- Guan, W.J., Ni, Z.Y., Hu, Y., et al. (2020). Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* *382*, 1708–1720.
- Gu, J., Gong, E., Zhang, B., et al. (2005). Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* *202*, 415–424.
- Gutiérrez-Ortiz, C., Méndez-Guerrero, A., Rodrigo-Rey, S., et al. (2020). Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* *95*, e601.
- He, L., Mäe, M.A., Muhl, L., et al. (2020). Pericyte-specific vascular expression of SARS-CoV-2 receptor ACE2—implications for microvascular inflammation and hypercoagulopathy in COVID-19. *bioRxiv*, <https://doi.org/10.1101/2020.05.11.088500>
- Helms, J., Kremer, S., Merdji, H., et al. (2020). Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med.* *382*, 2268–2270.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* *181*, 271–280.
- Huang, C., Wang, Y., Li, X., et al. (2020a). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* *395*, 497–506.
- Huang, Y.H., Jiang, D., and Huang, J.T. (2020b). SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav. Immun.* *87*, 149.
- Iadecola, C., Anrather, J., and Kamel, H. (2020). Effects of COVID-19 on the nervous system. *Cell* *183*, 16–27.

- Jacob, F., Pather, S.R., Huang, W.-K., et al. (2020). Human pluripotent stem cell-derived neural cells and brain organoids reveal SARS-CoV-2 neurotropism predominates in choroid plexus epithelium. *Cell Stem Cell* 27, 937–950.
- Jin, Y., Ji, W., Yang, H., et al. (2020). Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Signal Transduct. Target. Ther.* 5, 293.
- Kawakami, A., Kitsukawa, T., Takagi, S., et al. (1996). Developmentally regulated expression of a cell surface protein, neuropilin, in the mouse nervous system. *J. Neurobiol.* 29, 1–17.
- Klok, F.A., Kruijff, M.J.H.A., van der Meer, N.J.M., et al. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb. Res.* 191, 145–147.
- Kuo, C.-L., Pilling, L.C., Atkins, J.L., et al. (2020). APOE e4 genotype predicts severe COVID-19 in the UK biobank community cohort. *J. Gerontol. A Biol. Sci. Med. Sci.* 75, 2231–2232.
- Lechien, J.R., Chiesa-Estomba, C.M., De Siati, D.R., et al. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur. Arch. Otorhinolaryngol.* 277, 2251–2261.
- Li, K., Wohlford-Lenane, C., Perlman, S., et al. (2016). Middle East Respiratory Syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J. Infect. Dis.* 213, 712–722.
- Li, W., Moore, M.J., Vasilieva, N., et al. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 426, 450–454.
- Lu, R., Zhao, X., Li, J., et al. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 395, 565–574.
- Mao, L., Jin, H., Wang, M., et al. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 77, 683–690.
- Marta-Enguita, J., Rubio-Baines, I., and Gastón-Zubimendi, I. (2020). Fatal Guillain-Barré syndrome after infection with SARS-CoV-2. *Neurologia* 35, 265–267.
- Mehta, P., McAuley, D. F., Brown, M., et al. (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 395, 1033–1034.
- Meinhardt, J., Radke, J., Dittmayer, C., et al. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat. Neurosci.* 24, 168–175.
- Merkler, A.E., Parikh, N.S., Mir, S., et al. (2020). Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol.* 77, 1366–1372.
- Moriguchi, T., Harii, N., Goto, J., et al. (2020). A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94, 55–58.
- Najjar, S., Najjar, A., Chong, D.J., et al. (2020). Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. *J. Neuroinflammation* 17, 231.
- Netland, J., Meyerholz, D.K., Moore, S., et al. (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.
- Ouattara, L.A., Barin, F., Barthez, M.A., et al. (2011). Novel human reovirus isolated from children with acute necrotizing encephalopathy. *Emerg. Infect. Dis.* 17, 1436–1444.
- Oxley, T.J., Mocco, J., Majidi, S., et al. (2020). Large-vessel stroke as a presenting feature of Covid-19 in the young. *N. Engl. J. Med.* 382, e60.
- Pellegrini, L., Albecka, A., Mallery, D.L., et al. (2020). SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. *Cell Stem Cell* 27, 951–961.
- Peng, L., Liu, J., Xu, W., et al. (2020). SARS-CoV-2 can be detected in urine, blood, anal swabs, and oropharyngeal swabs specimens. *J. Med. Virol.* 92, 1676–1680.
- Pleasure, S.J., Green, A.J., and Josephson, S.A. (2020). The spectrum of neurologic disease in the severe acute respiratory syndrome Coronavirus 2 pandemic infection: neurologists move to the frontlines. *JAMA Neurol.* 77, 679–680.
- Politi, L.S., Salsano, E., and Grimaldi, M. (2020). Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol.* 77, 1028–1029.
- Pontelli, M., Castro, I., Martins, R., et al. (2020). Infection of human lymphomononuclear cells by SARS-CoV-2. *bioRxiv*, <https://doi.org/10.1101/2020.07.28.225912>
- Poyiadji, N., Shahin, G., Noujaim, D., et al. (2020). COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology* 296, e119–e120.
- Quirch, M., Lee, J., and Rehman, S. (2020). Hazards of the cytokine storm and cytokine-targeted therapy in patients with COVID-19: review. *J. Med. Internet. Res.* 22, e20193.
- Ramani, A., Müller, L., Ostermann, P.N., et al. (2020). SARS-CoV-2 targets neurons of 3D human brain organoids. *EMBO J.* 39, e106230.
- Rogers, J.P., Chesney, E., Oliver, D., et al. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 7, 611–627.
- Sedaghat, Z., and Karimi, N. (2020). Guillain Barre syndrome associated with COVID-19 infection: a case report. *J. Clin. Neurosci.* 76, 233–235.
- Shang, J., Wan, Y., Luo, C., et al. (2020). Cell entry mechanisms of SARS-CoV-2. *Proc. Natl Acad. Sci. USA* 117, 11727–11734.
- Sohal, S., and Mansur, M. (2020). COVID-19 presenting with seizures. *IDCases* 20, e00782.
- Song, E., Zhang, C., Israelow, B., et al. (2021). Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J. Exp. Med.* 218, e20202135.
- Spindler, K.R., and Hsu, T.-H. (2012). Viral disruption of the blood-brain barrier. *Trends Microbiol.* 20, 282–290.
- Suen, W.W., Prow, N.A., Hall, R.A., et al. (2014). Mechanism of West Nile virus neuroinvasion: a critical appraisal. *Viruses* 6, 2796–2825.
- Sun, S.-H., Chen, Q., Gu, H.-J., et al. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. *Cell Host Microbe* 28, 124–133.
- Toscano, G., Palmerini, F., Ravaglia, S., et al. (2020). Guillain-Barré syndrome associated with SARS-CoV-2. *N. Engl. J. Med.* 382, 2574–2576.
- Tseng, C.-T. K., Huang, C., Newman, P., et al. (2007). Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human Angiotensin-converting enzyme 2 virus receptor. *J. Virol.* 81, 1162–1173.
- Van den Pol, A.N. (2006). Viral infections in the developing and mature brain. *Trends Neurosci.* 29, 398–406.
- Varatharaj, A., Thomas, N., Ellul, M.A., et al. (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 7, 875–882.
- Viguier, A., Delamarre, L., Duplantier, J., et al. (2020). Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *J. Neuroradiol.* 47, 393–394.
- Walls, A.C., Park, Y.J., Tortorici, M.A., et al. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 181, 281–292.
- Wang, C., Zhang, M., Garcia, G., et al. (2021). ApoE-isoform-dependent SARS-CoV-2 neurotropism and cellular response. *Cell Stem Cell* 28, 331–342.
- Wang, Q., Zhang, Y., Wu, L., et al. (2020a). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell* 181, 894–904.
- Wang, W., Xu, Y., Gao, R., et al. (2020b). Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 323, 1843–1844.

- Yaghi, S., Ishida, K., Torres, J., et al. (2020). SARS-CoV-2 and stroke in a New York healthcare system. *Stroke* 51, 2002–2011.
- Yang, L., Han, Y., Nilsson-Payant, B.E., et al. (2020). A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell* 27, 125–136.
- Zanin, L., Saraceno, G., Panciani, P.P., et al. (2020). SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir.* 162, 1491–1494.
- Zhang, B.-Z., Chu, H., Han, S., et al. (2020). SARS-CoV-2 infects human neural progenitor cells and brain organoids. *Cell Res.* 30, 928–931.
- Zhang, T., Hirsh, E., Zandieh, S., et al. (2021). COVID-19-associated acute multi-infarct encephalopathy in an asymptomatic CADASIL patient. *Neurocrit. Care* 34, 1099–1102.
- Zhao, H., Shen, D., Zhou, H., et al. (2020a). Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 19, 383–384.
- Zhao, K., Huang, J., Dai, D., et al. (2020b). Acute myelitis after SARS-CoV-2 infection: a case report. medRxiv, <https://doi.org/10.1101/2020.03.16.20035105>
- Zhou, P., Yang, X.L., Wang, X.G., et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579, 270–273.
- Zubair, A.S., McAlpine, L.S., Gardin, T., et al. (2020). Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* 77, 1018–1027.