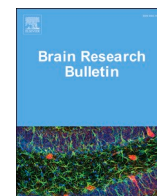




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Research report

Manifestations and mechanisms of central nervous system damage caused by SARS-CoV-2

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ABSTRACT

The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its threat to humans have drawn worldwide attention. The acute and long-term effects of SARS-CoV-2 on the nervous system pose major public health challenges. Patients with SARS-CoV-2 present diverse symptoms of the central nervous system. Exploring the mechanism of coronavirus damage to the nervous system is essential for reducing the long-term neurological complications of COVID-19. Despite rapid progress in characterizing SARS-CoV-2, the long-term effects of COVID-19 on the brain remain unclear. The possible mechanisms of SARS-CoV-2 injury to the central nervous system include: 1) direct injury of nerve cells, 2) activation of the immune system and inflammatory cytokines caused by systemic infection, 3) a high affinity of the SARS-CoV-2 spike glycoprotein for the angiotensin-converting enzyme ACE2, 4) cerebrovascular disease caused by hypoxia and coagulation dysfunction, and 5) a systemic inflammatory response that promotes cognitive impairment and neurodegenerative diseases. Although we do not fully understand the mechanism by which SARS-CoV-2 causes nerve injury, we hope to provide a framework by reviewing the clinical manifestations, complications, and possible mechanisms of neurological damage caused by SARS-CoV-2. With hope, this will facilitate the early identification, diagnosis, and treatment of possible neurological sequelae, which could contribute toward improving patient prognosis and preventing transmission.

1. Introduction

The coronavirus disease 2019 (COVID-19) epidemic has become the centre of global attention (Diseases TRJTLI, 2020). Coronaviruses are a large family of viruses that can infect both humans and animals. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family of *Coronaviridae* and causes symptoms similar to those of the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV). Since both coronaviruses act on the angiotensin-converting enzyme 2 (ACE2), the novel 2019 virus was named SARS-CoV-2 (Neurology GPJJo, 2020). SARS-CoV-2 causes COVID-19 disease, which manifests mainly as respiratory symptoms and pneumonia. Typical COVID-19 symptoms include fever, dry cough, and dyspnoea. Respiratory symptoms range from mild to severe, and the severity can progress from mild disease to

life-threatening acute respiratory distress syndrome (ARDS). SARS-CoV-2 infection can also affect the functions of the gastrointestinal tract, cardiovascular system, kidney, liver, and pancreas. Patients with severe disease are more likely to develop neurological symptoms, which range from headaches or dizziness to more serious convulsions and cerebrovascular disease (CVD) (LM et al., 2020). Autopsy reports have documented cerebral oedema and neuronal degeneration in patients with severe disease (H et al., 2020). In addition, acute seizures have been reported in two patients with severe COVID-19, which suggests that COVID-19 may cause central nervous system (CNS) damage (M et al., 2020). Since the on-going COVID-19 outbreak poses a huge threat to global public health, there is a need for clinical understanding of the effect of SARS-CoV-2 on the CNS with respect to prevention, diagnosis, and treatment. This review analyses cases that had neurological

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symptoms at the onset or during the course of COVID-19 and explores the possible mechanisms underlying CNS involvement. (Figs. 1–3).

2. Overview of SARS-CoV-2

Coronaviruses are enveloped RNA viruses with a single-stranded positive-sense RNA genome and a spherical or oval shaped envelope of 100 nm diameter. Structural proteins encoded by the genome of human coronaviruses include the spike, membrane, envelope, and nucleocapsid proteins. The nucleocapsid protein is highly conserved across coronaviruses and increasingly expressed during the infection process; it is therefore is a key antigen for virus detection (Li et al., 2003). The spike protein is crucially involved in the neurovirulence of SARS-CoV-2, the coronavirus entry into the brain, and it plays a role in tropism and regulation (Almazan et al., 2000). Spike proteins cover the coronavirus envelope and can bind to ACE2 protein in the heart, lungs, kidneys, and gastrointestinal tract, which facilitates virus entry into the target cells (Wu et al., 2020). Studies in mice found that the S1 subunit of the SARS-CoV-2 spike protein can cross the blood–brain barrier and bind to cells (Rhea et al., 2021). Among the seven known human coronaviruses, SARS-CoV-2, SARS-CoV, and the Middle East respiratory syndrome coronavirus each cause severe respiratory disease with high morbidity and mortality rates. There is 96% genomic similarity between SARS-CoV-2 and SARS-like bat coronaviruses (Wu et al., 2020). Consequently, SARS-CoV-2 is believed to have originated from bats, with Malayan pangolins being the intermediate host (Xiao et al., 2020). SARS-CoV-2 and SARS-CoV-1 share close sequence identity. A systematic comparison among viruses revealed that the functional and

pathogenic differences in SARS-CoV-2 could be attributed to amino acid substitutions (Wu et al., 2020). SARS-CoV-2 is transmitted via respiratory droplets, the digestive tract, and aerosols (Neurology GPJJo, 2020). It enters human cells by binding to the ACE2 protein, which is highly expressed in the airway epithelium, lung parenchyma, renal cells, and the cardiovascular and gastrointestinal systems; however, it has relatively low expression levels in the CNS (Wang et al., 2020). Neural studies on ACE2 expression in the brain have revealed that ACE2 is expressed mainly in the cortex but also on neurons and glial cells (Doobay et al., 2007; Alenina and Bader, 2019; Baig et al., 2020). Expression of ACE2 on glial cells and neurons in the brain may provide targets for the SARS-CoV-2 virus and lead to CNS infection. These findings indicate that ACE2 expression may be associated with the neurotropic potential of SARS-CoV-2 (Baig et al., 2020; Li et al., 2020; Wu et al., 2020). The neuroinvasion of SARS-CoV-2 indicates that the virus can spread from the respiratory tract to the CNS, and damage the CNS by directly replicating or through the host's immune response. In addition, SARS-CoV-2 can enter the CNS by infecting the endothelial cells of the blood–brain barrier or binding with ACE2 expressed on the endothelial cells. Moreover, the cytokine storm caused by SARS-CoV-2 infection can degrade the blood–brain barrier, increase its permeability, and lead to viral entry into the CNS through infected immune cells. Therefore, the neuropathological correlates of SARS-CoV-2 infection include hypoxic/ischemic encephalopathy, acute cerebrovascular disease, encephalitis/meningitis, acute myelitis, demyelinating disorders, etc. These are caused by abnormal immune response and secondary inflammatory tissue damage (Fisicaro et al., 2021).

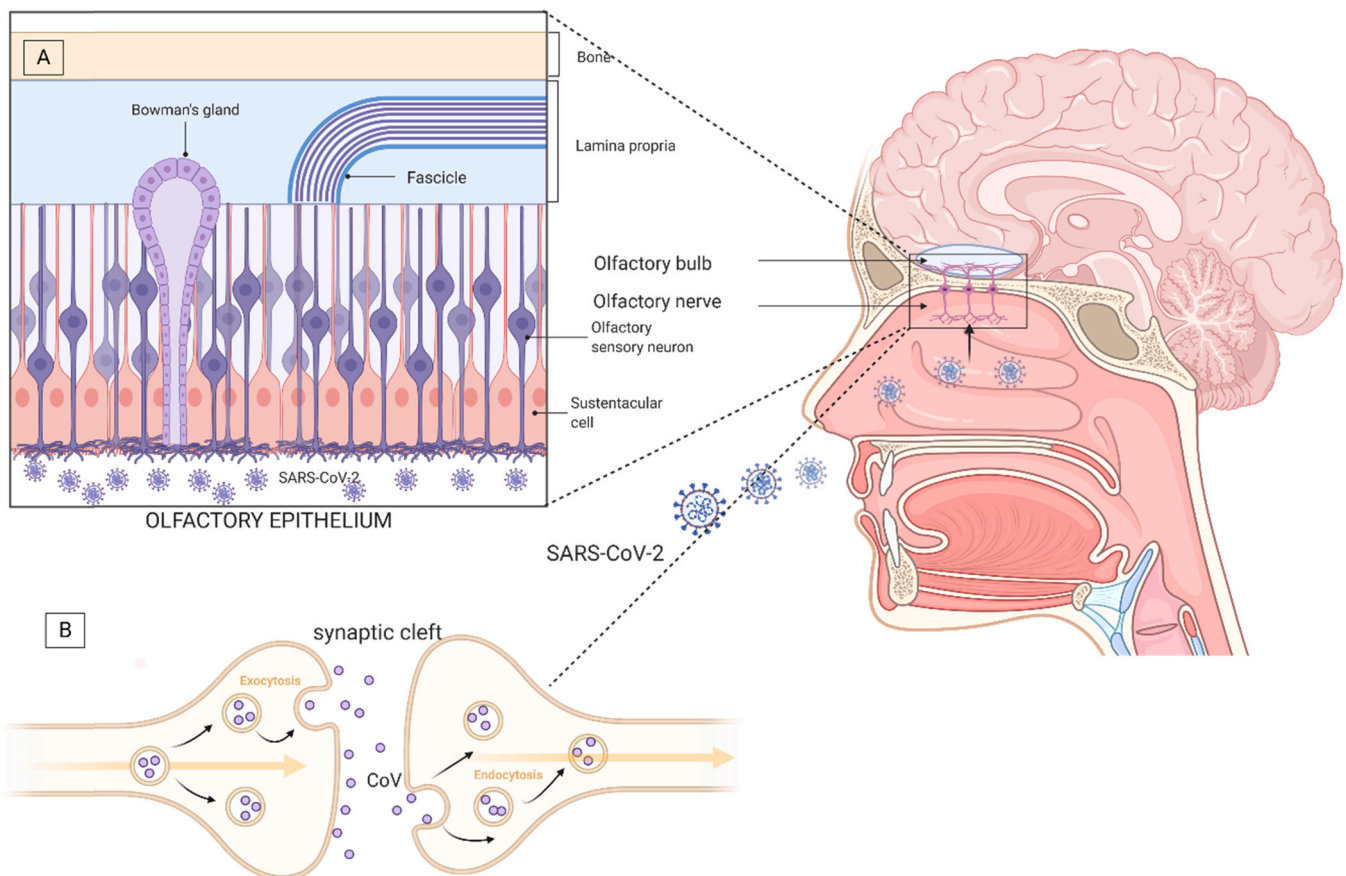


Fig. 1. Mechanism underlying SARS-CoV-2 damage to the CNS: the olfactory nerve pathway. A) SARS-CoV-2 infects sensory neurons of the olfactory epithelium in the nasal cavity. The olfactory sensory neurons extend axons to the olfactory bulb and pass the virus through the axonal transport mechanism to the CNS. B) SARS-CoV-2 can also spread to neuronal cell bodies through trans-synaptic transfer via exocytosis and endocytosis between synapses. This shows that SARS-CoV-2 can enter the CNS through the retrograde neuronal pathway. This figure was created by an author using the website <https://app.biorender.com>.

3. Search strategy and selection criteria

From June to August 2020, we systematically identified documents on the PubMed database regarding COVID-19 and related literature published until 31 July 2021. The following keywords were used in the search strategy to identify relevant topics: ‘SARS-CoV-2’ or ‘COVID-19’, and ‘central nervous system’, ‘brain’, ‘neurology’, ‘neurotropism’, ‘neuroinvasion’, ‘neurovirulence’, ‘long-term neurological sequelae’, or ‘nerve injury’. The selected documents served as the final reference list.

4. Clinical manifestations of nerve damage induced by SARS-CoV-2

The clinical manifestations of SARS-CoV-2 infections include fever, cough, pneumonia, and multiple organ dysfunction. A study on patients with COVID-19 in Wuhan, China reported that 36.4% (78/214 patients) presented CNS symptoms, including headaches, dizziness, and altered mental status (Huang et al., 2020; Guan et al., 2020). Moreover, some patients developed epilepsy, consciousness disorders, and CVD (Mao et al., 2020). The clinical manifestations of nervous system damage caused by SARS-CoV-2 also include olfactory and gustatory disorders, toxic-metabolic encephalopathy, and encephalitis.

4.1. Headache and dizziness

There is a relatively high incidence of headaches among patients with COVID-19 (Jin et al., 2020). A systematic review and analysis of 138 hospitalised patients with COVID-19 revealed 6.5–8.0% headache and 9.4% dizziness incidence rates (Rodríguez-Morales et al., 2020; Wang et al., 2020). The pathological association between headaches and COVID-19 remains unclear. Neuroinflammation caused by cytokines released by nociceptors in the nervous system can cause headaches; therefore, the mechanism underlying headaches in COVID-19 patients may involve cytokines and chemokines released by macrophages (Ye et al., 2020). A survey of patients with COVID-19 in Spain reported that 57.4% (483/841) of patients presented varying degrees of neurological

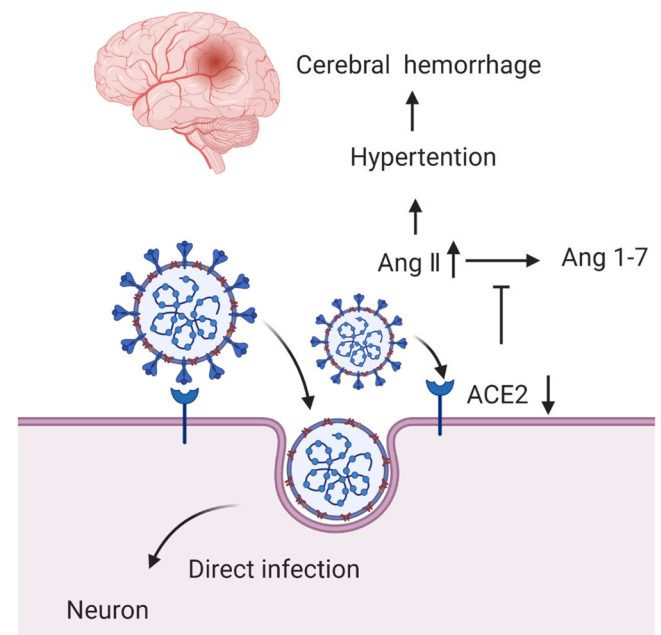


Fig. 3. Mechanism underlying SARS-CoV-2 damage to the CNS: direct infection route and dysfunction of the renin-angiotensin system. SARS-CoV-2 can directly infect host cells by binding to ACE2. Furthermore, viral infection can decrease ACE2 expression, which consequently inhibits angiotensin II cleavage, increases angiotensin II levels, and eventually results in hypertension and possible cerebral haemorrhage. This figure was created by an author using the website <https://app.biorender.com>.

symptoms, with headaches (14.1%, 119/841 patients) and dizziness (6.1%, 51/841 patients) being reported in the early stages of infection (Romero-Sanchez et al., 2020). A retrospective cohort study on confirmed COVID-19 cases reported that patients with headache had a lower risk of mortality. Moreover, the presence of headache was an

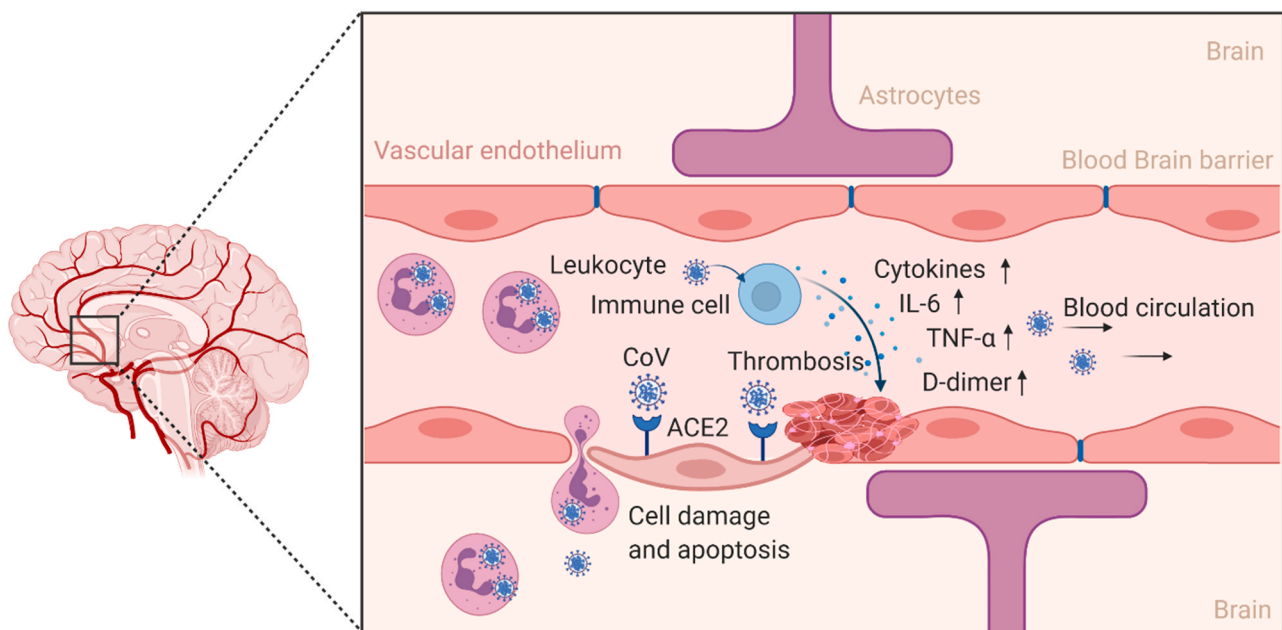


Fig. 2. Mechanism underlying SARS-CoV-2 damage to the CNS: the bloodborne and immune pathways. SARS-CoV-2 can enter the CNS by infecting the endothelial cells of the blood–brain barrier or binding with ACE2 expressed on endothelial cells. In addition, the cytokine storm caused by SARS-CoV-2 can destroy the blood–brain barrier, increase its permeability, and enter the CNS through infected immune cells. In addition, SARS-CoV-2 can enter the CNS through blood circulation. The virus-induced increase in cytokine levels could cause coagulopathies, which result in cerebral thrombosis or bleeding disorders. This figure was created by an author using the website <https://app.biorender.com>.

independent predictor for mortality risk among patients with COVID-19 (Trigo et al., 2020). There is a need for further studies to clarify the mechanism underlying the manifestation of neurological symptoms in COVID-19 patients. Clinicians should monitor neurological symptoms closely for prompt prevention of complications.

4.2. Olfactory and gustatory disorders

Olfactory and gustatory disorders are common clinical manifestations of COVID-19, with some studies suggesting a possible correlation between olfactory disorders and COVID-19 severity (Denis et al., 2020). A study on 72 patients with COVID-19 reported that they presented varying degrees of olfactory and gustatory disorders (Vaira et al., 2020). While children with COVID-19 often present mild respiratory symptoms, there are reports of children presenting with olfactory and gustatory disorders (Mak et al., 2020). A European survey on 72 patients with COVID-19 revealed that 74% (53 cases), 69% (50 cases), and 68% (49 cases) of the patients exhibited hyposmia, hypogeusia, or both symptoms, respectively. A recent autopsy report of two patients with severe COVID-19 revealed leukocyte infiltration and focal mucosal atrophy in the olfactory epithelium (Kirschenbaum et al., 2020). The pathophysiological mechanism underlying the SARS-CoV-2 effects on the olfactory system remains unclear; however, it may be related to ACE2 expression on the sustentacular and basal cells, which increases their virus susceptibility (Luerset al., 2020).

4.3. Disorders of consciousness

An analysis of 214 patients in Wuhan, China found that 78 (36.4%) cases presented with neurological manifestations. The most common symptoms were headache (16.8%, 36 cases) and dizziness (13.1%, 28 cases); patients with disorders of consciousness accounted for 16 (7.5%) cases. Severely ill patients were more prone to acute CVD, disorders of consciousness, and skeletal muscle injury (Mao et al., 2020). Disorders of consciousness in patients with COVID-19 may be associated with direct neuronal infection and subsequent damage of the brain parenchyma. Additionally, toxic encephalopathy, epilepsy, or demyelinating disease could cause impaired consciousness.

4.4. Toxic-metabolic encephalopathy

Patients with encephalopathy present mainly with delirium, lethargy, and impaired attention. A 53-year-old woman who was admitted due to cough, fever, and altered mental status was found to have acute haemorrhagic necrotising encephalopathy; magnetic resonance imaging showed haemorrhagic lesions (Poyiadji et al., 2020). Another study reported that among 82 confirmed cases of COVID-19 with neurological complications, 19 cases (23%) developed encephalitis or encephalopathy (Ghannam et al., 2020). A recent study describing three patients with COVID-19 who developed encephalitis or encephalopathy reported that their cerebrospinal fluid analysis showed elevated anti-S1 IgM levels; the levels of the interleukins IL-6, IL-8, and IL-10 were significantly increased, but the virus was not detected in the cerebrospinal fluid (Benameur et al., 2020). In another confirmed COVID-19 case, a 59-year-old woman with aplastic anaemia developed disorders of consciousness and epileptic seizures 10 days after presenting with fever, cough, and headache. Computed tomography revealed diffuse brainstem swelling and other lesions indicative of severe encephalopathy; the patient died on the eighth day of admission (Dixon et al., 2020). In another case of aplastic anaemia, the patient developed acute necrotising encephalopathy after SARS-CoV-2 infection with brainstem swelling and haemorrhagic lesions (Dixon et al., 2020). A prospective, multi-centre, observational study in New York found that 606 (13.5%) of 4491 patients infected with SARS-CoV-2 developed neurological diseases, including toxic-metabolic encephalopathy (6.8%), stroke (1.9%), and hypoxic/ischemic injury (1.4%) (Frontera et al., 2021).

4.5. Encephalitis

The first reported case of meningitis/encephalitis associated with SARS-CoV-2 was of a 24-year-old patient admitted due to convulsions with unconsciousness and seizures. A 60-year-old patient infected with SARS-CoV-2 presented only mild breathing abnormalities but developed encephalitis. Cerebrospinal fluid analysis revealed elevated IL-8 and tumour necrosis factor (TNF)- α levels, while electroencephalography exhibited generalised θ -wave slowing (Pilotto et al., 2020). A study on 29 patients with COVID-19 who required ventilator support in the intensive care unit (ICU) reported that six cases (20.6%) showed CNS involvement. Among them, magnetic resonance imaging revealed meningo-encephalitic lesions in three cases. Cerebrospinal fluid analysis did not detect pleocytosis, and virological testing was negative (L et al., 2020). Acute disseminated encephalomyelitis, a relatively rare immune-mediated CNS disease, has also been reported after SARS-CoV-2 infection (Novi et al., 2020).

4.6. Acute CVD

Between 23 March and 7 April 2020, five patients in New York aged < 50 years were diagnosed with COVID-19 and presented with new-onset symptoms of large-vessel ischaemic stroke; the average U.S. National Institutes of Health Stroke Scale score was 17 points (range: 0–42 points) (Oxley et al., 2020). A retrospective study on the COVID-19 epidemic in Wuhan, China reported that older patients with risk factors were more likely to develop CVD; 5% of hospitalised patients with COVID-19 developed acute ischaemic stroke, with the youngest patient being 55 years old (Li et al., 2020). A recent retrospective neuroimaging cohort study reported that patients with COVID-19 showed manifestations of vascular involvement in both the central and peripheral nervous systems (Klironomos et al., 2020). Patients with COVID-19 have increased plasminogen levels; plasminogen-related hyperfibrinolysis can increase D-dimer levels in severely ill patients and is often complicated by coagulopathy and vascular endothelial cell dysfunction (Ji et al., 2020; Zhou et al., 2020). Critically ill patients with COVID-19 are more susceptible to acute cerebrovascular events, which may be associated with severe thrombocytopenia and elevated D-dimer levels (Wang et al., 2020).

5. Possible mechanisms underlying nerve damage induced by SARS-CoV-2

5.1. Direct infection and damage

A recent report documented a 40-year-old woman with type 2 diabetes and obesity who was admitted to the hospital due to fever, syncope, and encephalitis. Cerebrospinal fluid analysis using a reverse transcription-polymerase chain reaction was positive for SARS-CoV-2 (Huang et al., 2020). Consequently, this was considered a case of SARS-CoV-2 encephalitis. Since the SARS-CoV-2 infection was confined entirely to the CNS, and there was no involvement of other organ systems, it was speculated to have been caused by direct viral infection of the CNS. There is also a recent report of SARS-CoV-2 being detectable in the brains of humans and mice, suggesting that SARS-CoV-2 has a neuroinvasive capacity and can infect neurons directly (Song et al., 2021). However, there are reports of virus being undetectable in the cerebrospinal fluid of patients infected with SARS-CoV-2, which might be related to systemic disease severity and viral neurotropism (Espínola et al., 2020; Toscano et al., 2020; Gutiérrez-Ortiz et al., 2020). The presence of SARS-CoV-2 in the cerebrospinal fluid remains a controversial topic that requires further investigation (Al Saiegh et al., 2020).

5.2. Retrograde neuronal pathways

By infecting peripheral neurons, viruses can gain access to the CNS

through axonal transport mechanisms (Desforgues et al., 2019; Zubair et al., 2020). Viruses can infect sensory or motor nerve endings and achieve retro- or anterograde neuronal transport (Leite et al., 2015). The nasal respiratory tract is the main route for SARS-CoV-2 transmission. In a summary report on 72,314 cases, the Chinese Centre for Disease Control and Prevention showed that 62% of 44,672 confirmed cases of COVID-19 had positive viral nucleic acid tests of throat swab samples (Wu and McGoogan, 2020). The olfactory nerve is composed of olfactory sensory neurons, which have dendrites that project into the nasal cavity; moreover, axons extend to the olfactory bulb via the cribriform plate. Although the olfactory bulb can effectively control viral entry into the CNS (Durrant et al., 2016), coronaviruses can enter the brain through the olfactory mucosa and olfactory tract during the early infection stages (M et al., 2019; Yates, 2021). Research has shown that olfactory bulb ablation can limit CNS invasion by coronaviruses (Bohmwald et al., 2018; Meinhardt et al., 2021). This suggests that the olfactory nerve and olfactory bulb provide CNS entry for many viruses (van Riel et al., 2015). A recent study found that the SARS-CoV-2 virus was detected in the olfactory neurons of COVID-19 patients (Lemprière, 2021). These results indicate that coronaviruses can gain access to the CNS via retrograde neuronal transmission.

5.3. Bloodborne pathways

Viruses can enter the CNS and other sites by infecting leukocytes or the endothelial cells of the blood–brain barrier (M et al., 2019; Desforgues et al., 2014; Berth et al., 2009). The blood–brain barrier is composed of vascular endothelial cells, astrocytes, pericytes, and the extracellular matrix. Since all vascular endothelial cells can express ACE2, SARS-CoV-2 can enter the CNS by binding to this membrane-bound enzyme on the capillary endothelial cells of the blood–brain barrier (Baig et al., 2020). Additionally, viruses can cross the blood–brain barrier by infecting peripheral leukocytes that enter the CNS through blood circulation. Systemic inflammatory cytokines, chemokines, and other soluble mediators induced by SARS-CoV-2 may also damage the blood–brain barrier, which increases its permeability and, thus, allows entry of viruses and infected immune cells into the CNS (Sankowski et al., 2015).

5.4. Immune pathways

The antiviral immune response is crucial for pathogen elimination from the body. However, the cytokine storm resulting from excessive and abnormal host immune response can cause systemic inflammatory response syndrome. Increased inflammatory cytokine levels can also cause cognitive decline (Heneka et al., 2020). SARS-CoV-2 infection of epithelial cells, dendritic cells, and macrophages of the respiratory tract induces secretion of antiviral factors (interferons), pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α), and chemokines (Ye et al., 2020). Another study reported that compared with mildly ill patients, severely ill patients showed significantly elevated levels of serum granulocyte colony-stimulatory factor (G-CSF), IP-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1 α , and TNF- α . These studies indicate a positive correlation between cytokine storms and disease severity (Huang et al., 2020). There is increasing evidence that patients with severe COVID-19 may experience such a cytokine storm (Mehta et al., 2020; Kempuraj et al., 2020). Compared to non-ICU patients, critically ill ICU patients were found to have higher plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1 α , and TNF- α ; this suggests that the presence of cytokine storms is related to disease severity (Huang et al., 2020).

Viral replication may cause epithelial and endothelial cell apoptosis, as well as vascular leakage, and therefore trigger the release of pro-inflammatory cytokines and chemokines (Fu et al., 2020). Critically ill patients often present increased IL-6 and IL-8 levels, as well as decreased lymphocyte counts, especially for CD4- and CD8-positive cells, which

can predict disease characteristics and progression. The impairment of immune cytotoxic functions is dependent on IL-6 (Mazzoni et al., 2020); additionally, IL-6 may serve as a biomarker for early detection of COVID-19 progression (Zhang et al., 2020; Blanco-Melo et al., 2020; Herold et al., 2020; Wang et al., 2020). The activation of immune cells and the increase of inflammatory factors may cause chronic inflammation of the brain and CNS complications. Moreover, tocilizumab (an IL-6 receptor blocker) can control the COVID-19-induced cytokine storm to a certain extent (Authors et al., 2020). Immune cell activation can cause chronic inflammation and nerve damage in the brain. In summary, these results show that SARS-CoV-2 can trigger cytokine storms and neuro-inflammatory responses by activating mast cells, neurons, glial cells, and endothelial cells (Kempuraj et al., 2020).

5.5. Hypoxic injury and coagulopathy

Pulmonary inflammation in patients with SARS-CoV-2 can impair gas exchange, which leads to hypoxia in the CNS followed by cerebral vasodilation and interstitial oedema. Patients with COVID-19 may develop venous or arterial thromboembolism resulting from inflammation and hypoxia; this can cause complications that include ischaemic stroke, myocardial infarction, and pulmonary embolism (Klok et al., 2020; Dharmoon et al., 2021). Patients with COVID-19 may develop coagulopathies caused by cytokine storms or sepsis, which can cause stroke (Hess et al., 2020). Sepsis-induced coagulopathy is a precursor to disseminated intravascular coagulation, which can result in prolonged prothrombin time, elevated D-dimer levels, and thrombocytopenia with subsequent endothelial dysfunction and microthrombosis (Iba et al., 2019). A retrospective cohort study on 466 patients with COVID-19 reported that critically ill patients had significantly increased occurrences of thrombocytopenia, prothrombin time, and levels of D-dimer and fibrin degradation products (Liao et al., 2020). Most fatal cases of severely ill COVID-19 patients involved intracranial haemorrhage or pulmonary embolism (von Weyhern et al., 2020), which is consistent with COVID-19-induced coagulopathy (Zhang et al., 2020). Recent animal studies also suggest that severe SARS-CoV-2-infected mice developed thrombosis and vascular inflammation (Zheng et al., 2021).

5.6. ACE2

ACE2 is an important element of the renin-angiotensin-aldosterone system. It is widely expressed in the human lung parenchyma, airway epithelium, kidneys, small intestine, and vascular endothelial cells; thus, it can be found throughout the body and CNS (Zubair et al., 2020; Li et al., 2020). ACE2 counters the effects of ACE1 and angiotensin-II, and therefore exerts cardiovascular protective effects. The spike protein of SARS-CoV-2 has a high affinity for ACE2, which makes ACE2 a key target for vaccine and antibody development (Wrapp et al., 2020). The strong affinity of SARS-CoV-2 to the human ACE2 protein has resulted in its high pathogenicity (Gheblawi et al., 2020). Previous studies have detected ACE2 activity in the human cerebrospinal fluid; a recent immunocytochemistry study using mixed neurons derived from human pluripotent stem cells reported found high ACE2 expression in neuronal cell bodies and lesser expression in axons and dendrites (Xu and Lazartigues, 2020). Although this study did not use human brain tissue, it provides evidence of neuronal expression of ACE2 that makes neurons a possible target for SARS-CoV-2 (Xu and Lazartigues, 2020). Infection of a mouse model expressing human ACE2 protein with SARS-CoV-2 showed high viral loads in the lungs, trachea, and brain (Sun et al., 2020). SARS-CoV-2 binding to ACE2 may abnormally increase blood pressure and consequently increase the risk of cerebral haemorrhage. Moreover, SARS-CoV-2 can access the CNS by binding to ACE2 protein on vascular endothelial cells of the blood–brain barrier (Baig et al., 2020; Desforgues et al., 2019). Since ACE inhibitors result in increased ACE2 expression, future studies could explore whether patients with hypertension and diabetes who use ACE inhibitors are more susceptible

to SARS-CoV-2 infection (Nath, 2020).

5.7. Long-term sequelae of nervous system and possible mechanisms

Although various countries are actively developing antiviral drugs and vaccines, the long-term nervous system sequelae caused by SARS-CoV-2 is attracting more and more attention (Miners et al., 2020; Bougakov et al., 2021; Ellul et al., 2020). In the follow-up of 797 patients, 509 patients had sequelae within 6 months after discharge; neurological sequelae accounted for 20.8% (Romero-Duarte et al., 2021). From January 17 to August 4, 2020, a prospective, multicentre cohort study of 73197 hospitalized COVID-19 patients in the UK found that 4.3% (3115 patients) had neurological complications (Drake et al., 2021). Studies have shown that the direct or indirect injury of neurons by SARS-CoV-2 can cause mental disorders and cognitive impairment of nervous system (Kumar et al., 2021; Pun et al., 2021; de Erausquin et al., 2021). The magnetic resonance imaging of 51 patients with COVID-19 taken 3 months after discharge was analysed (Qin et al., 2021) and, compared with the healthy control group, severe patients appeared to have indirect damage to the brain related to inflammatory factors (e.g., C-reactive protein, procalcitonin, and IL-6), especially in the thickness of the cerebral cortex; decreased cerebral blood flow and white matter microstructure changes are more serious, causing changes in brain volume, blood flow and white matter tracts, which may be one of the reasons for the long-term sequelae of the nervous system. In an investigation of 29 cognitively impaired COVID-19 patients, performed 3–4 months after discharge, it was found that language learning and executive functions were the most affected. Such patients should be systematically screened and targeted treatment (Miskowiak et al., 2021). The problem of cognitive impairment still requires further research (Hewitt et al., 2021). Six months after acute infection, COVID-19 survivors are mainly troubled by fatigue or muscle weakness, sleep difficulties, and anxiety or depression; these are the main targets of long-term rehabilitation intervention (Huang et al., 2021). In addition, studies have shown that about 30% of patients diagnosed with COVID-19 report persistent olfactory dysfunction (D'Ascanio et al., 2021). A follow-up survey conducted on 55 COVID-19 subjects who experienced a loss of smell between the end of February and the beginning of March 2020 found that 91% of the patients recovered their sense of smell after eight months, 53% of which were fully recovered (Capelli and Gatti, 2021). COVID-19 infection has a greater effect on patients with pre-existing neurological diseases; patients with Alzheimer's disease and dementia have a relatively higher risk of severe COVID-19 infection and neuropsychiatric disorders (Numbers and Brodaty, 2021).

ACE2 is widely expressed in cerebral vascular endothelial cells. The high affinity of SARS-CoV-2 spike glycoprotein for ACE2 can damage the integrity of the blood–brain barrier to varying degrees (Pezzini and Padovani, 2020). In addition, cytokine storms, hypoxia, and coagulopathy can all reduce the integrity of the blood–brain barrier; any one or a combination of these could become the potential basis for long-term sequelae of the nervous system (Wang et al., 2020, Heneka et al., 2020). Systemic inflammation can cause cognitive decline and neurodegenerative diseases (Remsik et al., 2021), which may result in neurodegeneration in patients with COVID-19 in the next few years (Iwashyna et al., 2010; Widmann and Heneka, 2014). COVID-19 patients are likely to have activation of the NLRP3 inflammasome (Heneka et al., 2020), which can directly induce or aggravate the neurodegenerative process that leads to Alzheimer's disease (Heneka et al., 2013). In addition, NLRP3-driven and IL-1 β -mediated regulation of phosphokinases and phosphatases play a role in the pathological formation of neurofibrillary tangles, which may induce or aggravate neurodegeneration in patients with COVID-19 (Ising et al., 2019). Studies have revealed that the ACE2 protein in the brain of Alzheimer's disease patients is up-regulated, and there is a moderately positive correlation between the increased expression of ACE2 protein and oxidative stress (Ding et al., 2021). This could be one possible factor related to the

long-term nervous system sequelae caused by the SARS-CoV-2 virus.

6. Conclusion

The effects of SARS-CoV-2 on the CNS may cause acute and long-term changes of the nervous system or aggravate existing neurological diseases or symptoms. Long COVID refers to diseases in people that have recovered from COVID-19 infection but are still affected by the persistence of infection, or that the duration of symptoms is much longer than expected. Long-term COVID can affect several systems, including the respiratory system, cardiovascular system, and nervous system. Patients experience symptoms that include fatigue, dyspnoea, cardiac abnormalities, cognitive impairment, sleep disorders, post-traumatic stress disorder, muscle pain, concentration problems, and headaches (Crook et al., 2021). SARS-CoV-2 neuropathology-related factors include the SARS-CoV-2 spike protein binding with ACE2 on host cells; SARS-CoV-2 can interrupt the ACE/ACE2 balance and activate the renin angiotensin aldosterone system activation, leading to disease progression in patients with hypertension, diabetes, and cardiovascular disease. SARS-CoV-2 can enter the CNS through the blood–brain barrier through the blood-derived pathway, and systemic inflammatory response will further increase the permeability of the blood–brain barrier; this promotes the invasion of infected immune cells into the CNS. Immune responses and inflammatory mediators can also neuropathologically cause brain injury. Because of COVID-related hypoxia, the increase of inflammatory factors and coagulation dysfunction caused by SARS-CoV-2 will increase the incidence of cerebrovascular disease; therefore, reducing hypoxia and protecting the brain from cytokines are important therapeutic goals. Because SARS-CoV-2 can activate the immune system and increase systemic inflammatory factors, immunomodulatory interventions may be needed in COVID-19 patients in the future to reduce the acute and long-term nervous system complications related to SARS-CoV-2 infection.

In future research, determining how to reduce the nervous system invasion and neurotoxicity of SARS-CoV-2 through drugs is a problem that needs to be solved. This long-term work requires personal efforts, government intervention, and full cooperation among countries to minimize the infection rate. In the future, people will have to monitor the effects of COVID-19 on the human nervous system for a long time to make detailed assessments, diagnoses, and treatment plans. Future studies need to clarify the effects of SARS-CoV-2 on human cognitive function and neurodegenerative diseases. Clarification of the mechanism of SARS-CoV-2 on the brain needs to be combined with the study of delayed neuropsychiatric sequelae; this will require a large amount of worldwide clinical epidemiological data. Clinical and basic research also needs to be promoted; in particular, nonspecific neurological complications caused by hypoxic encephalopathy need to be distinguished from neurological manifestations that are directly or indirectly caused by viruses (Ellul et al., 2020). For patients with COVID pneumonia with a neurological symptom as the first symptom, timely diagnosis and identification are of great importance in preventing sequelae in the nervous system. Further research should focus on elucidating the pathophysiology and risk factors for COVID-19-related neurological complications to improve its prognosis, as well as reduce its social, medical, and economic burdens.

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CRediT authorship contribution statement

Fan Yang: Devised the idea for this review and prepared the initial manuscript draft., **Hai Zhao:** Collected and analysed the literature, **Hongtao Liu:** Collected and analysed the literature, **Xiuying Wu:**

Designed and drafted the figures, **Yongnan Li**: Wrote and revised the initial manuscript.

All authors contributed equally to this work. They reviewed and approved the final draft of the manuscript.

Declaration of Competing Interest

All authors declare that there are no conflicts of interests.

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References

- 2020 Cytokine Storm Drugs Move from CAR T to COVID-19. *%J Cancer discovery*. 2020, 10(7): OF8.
- Rodriguez-Morales, A.J., et al., 2020. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med. Infect. Dis.*
- Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., Meng, J., Zhu, Z., Zhang, Z., Wang, J., Sheng, J., Quan, L., Xia, Z., Tan, W., Cheng, G., Jiang, T., 2020. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 27, 325–328.
- Baig, A., Khaleeq, A., Ali, U., Syeda, H., 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem. Neurosci.* 11 (7), 995–998.
- Berth, S., Leopold, P., Morfini, G.J., 2009. Virus-induced neuronal dysfunction and degeneration. *Front. Biosci.* 14, 5239–5259.
- Blanco-Melo D., Nilsson-Payant B., Liu W., Uhl S., Hoagland D., Møller R., et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. 2020, 181(5): 1036–1045.e1039.
- Bohmwald, K., Gálvez, N., Ríos, M., Kalergis, A.J., 2018. Neurologic alterations due to respiratory virus infections. *Front. Cell. Neurosci.* 12, 386.
- Bougakov, D., Podell, K., Goldberg, E., 2021. Multiple neuroinvasive pathways in COVID-19. *Mol. Neurobiol.* 58 (2), 564–575.
- Capelli, M., Gatti, P., 2021. Anosmia in the first coronavirus disease 2019 outbreak in Europe: functional recovery after eight months. *J. Laryngol. Otol.* 135 (3), 224–228.
- Romero-Sanchez, C.M., et al., 2020. Neurologic manifestations in hospitalized patients with COVID-19: the ALBA COVID registry. *Neurology* 95.
- Crook, H., Raza, S., Nowell, J., Young, M., Edison, P., 2021. Long covid-mechanisms, risk factors, and management. *BMJ* 374, 1648.
- Huang, C., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395, 497–506.
- D'Ascanio, L., Vitelli, F., Cingolani, C., Maranzano, M., Brenner, M.J., Di, Stadio, A., 2021. Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results. *Eur. Rev. Med. Pharmacol. Sci.* 25 (11), 4156–4162.
- Desforges, M., Le Coupanec, A., Dubeau, P., Bourgoign, A., Lajoie, L., Dubé, M., Talbot, P.J., 2019. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 12 (1).
- Desforges, M., Le Coupanec, A., Stodola, J., Meessen-Pinard, M., Talbot, P.J., 2014. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.* 194, 145–158.
- Dharmoon, M.S., Thaler, A., Gururangan, K., Kohli, A., Sisiniega, D., Wheelwright, D., Mensching, C., Fifi, J.T., Fara, M.G., Jette, N., Cohen, E., Dave, P., DiRisio, A.C., Goldstein, J., Loebel, E.M., Mayman, N.A., Sharma, A., Thomas, D.S., Vega Perez, R. D., Weingarten, M.R., Wen, H.H., Tuhim, S., Stein, L.K., Mount Sinai Stroke, I., 2021. Acute Cerebrovascular Events With COVID-19 Infection. *Stroke* 52 (1), 48–56.
- Ding, Q., Shults, N.V., Gychka, S.G., Harris, B.T., Suzuki, Y.J., 2021. Protein expression of angiotensin-converting enzyme 2 (ACE2) is upregulated in brains with Alzheimer's disease. *Int. J. Mol. Sci.* 22 (4).
- Diseases TRJTLI. Pandemic potential of 2019-nCoV. 2020, 20(3): 280.
- Drake, T.M., Riad, A.M., Fairfield, C.J., Egan, C., Knight, S.R., Pius, R., Hardwick, H.E., Norman, L., Shaw, C.A., McLean, K.A., Thompson, A., Ho, A., Swann, O.V., Sullivan, M., Soares, F., Holden, K.A., Merson, L., Plotkin, D., Sigfrid, L., de Silva, T. I., Girvan, M., Jackson, C., Russell, C.D., Dunning, J., Solomon, T., Carson, G., Olliaro, P., Nguyen-Van-Tam, J.S., Turtle, L., Docherty, A.B., Openshaw, P.J., Baillie, J.K., Harrison, E.M., Semple, M.G., investigators, 2021. Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: a prospective, multicentre cohort study. *Lancet* 398 (10296), 223–237.
- Durrant, D.M., Ghosh, S., Klein, R.S., 2016. The olfactory bulb: an immunosensory effector organ during neurotropic viral infections. *ACS Chem. Neurosci.* 7 (4), 464–469.
- Wang, Dawei, Hu, Bo, Hu, Chang et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. 2020.
- Ellul, M.A., Benjamin, L., Singh, B., Lant, S., Michael, B.D., Easton, A., Kneen, R., Defres, S., Sejvar, J., Solomon, T., 2020. Neurological associations of COVID-19. *Lancet Neurol.* 19 (9), 767–783.
- Ellul, M.A., Benjamin, L., Singh, B., Lant, S., Michael, B.D., Easton, A., Kneen, R., Defres, S., Sejvar, J., Solomon, T., 2020. Neurological associations of COVID-19. *Lancet Neurol.* 19, 767–783.
- de Erausquin, G.A., Snyder, H., Carrillo, M., Hosseini, A.A., Brugha, T.S., Seshadri, S., 2021. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. *Alzheimer's Dementia: J. Alzheimer's Assoc.* 17 (6), 1056–1065.
- Espíndola, O.M., Siqueira, M., Soares, C.N., Lima, M., Leite, A., Araujo, A.Q.C., Brandão, C.O., Silva, M., 2020. Patients with COVID-19 and neurological manifestations show undetectable SARS-CoV-2 RNA levels in the cerebrospinal fluid. *Int. J. Infect. Dis.* 96, 567–569.
- Fiscaro, F., Di Napoli, M., Liberto, A., Fanella, M., Di Stasio, F., Pennisi, M., Bella, R., Lanza, G., Mansueto, G., 2021. Neurological sequelae in patients with COVID-19: a histopathological perspective. *Int. J. Environ. Res. Public Health* 18 (4).
- Frontera, J.A., Sabadia, S., Lalchan, R., Fang, T., Flusty, B., Millar-Vernetti, P., Snyder, T., Berger, S., Yang, D., Granger, A., Morgan, N., Patel, P., Gutman, J., Melmed, K., Agarwal, S., Bokhari, M., Andino, A., Valdes, E., Omari, M., Kvernland, A., Lillemo, K., Chou, S.H., McNett, M., Helbok, R., Mainali, S., Fink, E.L., Robertson, C., Schober, M., Suarez, J.L., Ziai, W., Menon, D., Friedman, D., Friedman, D., Holmes, M., Huang, J., Thawani, S., Howard, J., Abou-Fayssal, N., Krieger, P., Lewis, A., Lord, A.S., Zhou, T., Kahn, D.E., Czeisler, B.M., Torres, J., Yaghi, S., Ishida, K., Scher, E., de Havenon, A., Placantonakis, D., Liu, M., Wisniewski, T., Troxel, A.B., Balcer, L., Galetta, S., 2021. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. *Neurology* 96 (4), e575–e586.
- Fu, Y., Cheng, Y., Wu, Y., 2020. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virol. Sin.* 35, 266–271.
- Almazan, F., Gonzalez, J.M., Penzes, Z., Izeta, A., Calvo, E., Plana-Duran, J., Enjuanes, L., 2000. Engineering the largest RNA virus genome as an infectious bacterial artificial chromosome. *Proc. Natl. Acad. Sci. U.S.A.* 97, 5516–5521.
- Al Saiegh, F., Ghosh, R., Leibold, A., Avery, M.B., Schmidt, R.F., Theofanis, T., Mouchtouris, N., Philipp, L., Peiper, S.C., Wang, Z.X., Rincon, F., Tjoumakaris, S., Jabbour, P., Rosenwasser, R.H., Gooch, M.R., 2020. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J. Neurol. Neurosurg. Psychiatry* 91, 846–848.
- Denis, F., Galmiche, S., Dinh, A., Fontanet, A., Scherpereel, A., Benezit, F., Lescuré, F.X., 2020. Epidemiological observations on the association between anosmia and COVID-19 infection: analysis of data from a self-assessment web application. *J. Med. Internet Res.* 22, e19855.
- Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J.C., Turner, A.J., Raizada, M. K., Grant, M.B., Oudit, G.Y., 2020. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system. *Circ. Res.* 126, 1456–1474.
- Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D., Du, B., Li, L.J., Zeng, G., Yuen, K.Y., Chen, R.C., Tang, C.L., Wang, T., Chen, P.Y., Xiang, J., Li, S.Y., Wang, J.L., Liang, Z.J., Peng, Y.X., Wei, L., Liu, Y., Hu, Y.H., Peng, P., Wang, J.M., Liu, J.Y., Chen, Z., Li, G., Zheng, Z.J., Qiu, S.Q., Luo, J., Ye, C.J., Zhu, S.Y., Zhong, N.S., 2020. Clinical characteristics of coronavirus disease 2019 in China. *New Engl. J. Med.* 382 (18), 1708–1720.
- Gutiérrez-Ortiz, C., Méndez-Guerrero, A., Rodrigo-Rey, S., San Pedro-Murillo, E., Bermejo-Guerrero, L., Gordo-Mañas, R., de Aragón-Gómez, F., Benito-León, J., 2020. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 95 (5), 601.
- Heneka, M.T., Golenbock, D., Latz, E., Morgan, D., Brown, R., 2020. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Res. Ther.* 12 (1), 69.

- Heneka, M.T., Kummer, M.P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T.C., Gelpi, E., Halle, A., Korte, M., Latz, E., Golenbock, D.T., 2013. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 493 (7434), 674–678.
- Herold, T., Jurinovic, V., Arnreich, C., Lipworth, B.J., Hellmuth, J.C., von Bergwelt-Baildon, M., Klein, M., Weinberger, T., 2020. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J. Allergy Clin. Immunol.* 146.
- Hess D., Eldahshan W., Rutkowski EJTr. COVID-19-Related Stroke. 2020, 11(3): 322–325.
- Hewitt, K.C., Marra, D.E., Block, C., Cysique, L.A., Drane, D.L., Haddad, M.M., Lojek, E., McDonald, C.R., Reyes, A., Eversole, K., Bowers, D., 2021. Central nervous system manifestations of COVID-19: a critical review and proposed research agenda. *J. Int. Neuropsychol. Soc.*: JINS 1–15.
- Ji, H.L., Zhao, R., Matalon, S., Matthay, M.A., 2020. Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. *Physiol. Rev.* 100 (3), 1065–1075.
- Huang, C., Huang, L., Wang, Y., Li, X., Ren, L., Gu, X., Kang, L., Guo, L., Liu, M., Zhou, X., Luo, J., Huang, Z., Tu, S., Zhao, Y., Chen, L., Xu, D., Li, Y., Li, C., Peng, L., Li, Y., Xie, W., Cui, D., Shang, L., Fan, G., Xu, J., Wang, G., Wang, Y., Zhong, J., Wang, C., Wang, J., Zhang, D., Cao, B., 2021. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet (London, England)* 397 (10270), 220–232.
- Zhao, H., Shen, D., Zhou, H., Liu, J., Chen, S., 2020. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 19, 383–384.
- Iba, T., Levy, J.H., Warkentin, T.E., Thachil, J., Van der Poll, T., Levi, M., 2019. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J. Thromb. Haemost.*
- Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S.V., Vieira-Saecker, A., Schwartz, S., Albasset, S., McManus, R.M., Tejera, D., Griep, A., Santarelli, F., Brosseron, F., Opitz, S., Stunden, J., Merten, M., Kaye, R., Golenbock, D.T., Blum, D., Latz, E., Bué, L., Heneka, M.T., 2019. NLRP3 inflammasome activation drives tau pathology. *Nature* 575 (7784), 669–673.
- Iwashyna, T.J., Ely, E.W., Smith, D.M., Langa, K.M., 2010. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Jama* 304 (16), 1787–1794.
- Luers, J.C., Rokohl, A.C., Loreck, N., Wawer Matos, P.A., Augustin, M., Dewald, F., Klein, F., Lehmann, C., Heindl, L.M., 2020. Olfactory and gustatory dysfunction in coronavirus disease 2019 (COVID-19). *Clin. Infect. Dis.* 71.
- Kempuraj, D., Selvakumar, G.P., Ahmed, M.E., Raikwar, S.P., Thangavel, R., Khan, A., Zaheer, S.A., Iyer, S.S., Burton, C., James, D., Zaheer, A., 2020. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. *Neurosci.: Rev. J. Bring. Neurobiol. Neurol. Psychiatry* 26 (5–6), 402–414.
- Kempuraj, D., Selvakumar, G.P., Ahmed, M.E., Raikwar, S.P., Thangavel, R., Khan, A., Zaheer, S.A., Iyer, S.S., Burton, C., James, D., Zaheer, A., 2020. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. *Neuroscientist* 26.
- Kirschenbaum, D., Imbach, L.L., Ulrich, S., Rushing, E.J., Keller, E., Reimann, R.R., Frauenknecht, K., Lichtblau, M., Witt, M., Hummel, T., Steiger, P., Aguzzi, A., Frontzek, K., 2020. Inflammatory olfactory neuropathy in two patients with COVID-19. *Lancet* 396 (10245), 166.
- Klironomos, S., Tzortzakakis, A., Kits, A., Öhberg, C., Kollia, E., Ahomazda, A., et al., 2020. Nervous system involvement in coronavirus disease 2019: results from a retrospective consecutive neuroimaging cohort. *Radiology* 297, 202791.
- Klok, F.A., Kruip, M.J.H.A., van der Meer, N.J.M., Arbous, M.S., Gommers, D.A.M.P.J., Kant, K.M., et al., 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb. Res.* 191.
- Kumar, S., Veldhuis, A., Malhotra, T., 2021. Neuropsychiatric and cognitive sequelae of COVID-19. *Front. Psychol.* 12, 577529.
- Benamer, K., Agarwal, A., Auld, S.C., Butters, M.P., Webster, A.S., Ozturk, T., et al., 2020. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg. Infect. Dis.* 26.
- Xiao, K., Zhai, J., Feng, Y., Zhou, N., Zhang, X., Zou, J.J., et al., 2020. Isolation of SARS-CoV-2-related coronavirus from Malaysian pangolins. *Nature* 583.
- Vaira, L.A., Deiana, G., Giuseppe Fois, A., Pirina, P., Madeddu, G., De Vito, A., et al., 2020. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck* 42, 1252–1258.
- Lemprière, S., 2021. SARS-CoV-2 detected in olfactory neurons. *Nature Rev. Neurol.* 17 (2), 63.
- Liao, D., Zhou, F., Luo, L., 2020. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. *Lancet Haematol.*
- Li, Y., Li, M., Wang, M., et al., 2020. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc. Neurol.* 5.
- Li, M.Y., Li, L., Zhang, Y., Wang, X.S., 2020. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect. Dis. Poverty.*
- Mao, L., Jin, H., Wang, M., 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 77.
- Dogan, L., Kaya, D., Sarikaya, T., et al., 2020. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. *Brain Behav. Immun.* 87, 155–158.
- Dixon, L., Varley, J., Gontsarova, A., 2020. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol. Neuroimmunol. Neuroinflamm.*
- Mak, P.Q., Chung, K.S., Wong, J.S., Shek, C.C., Kwan, M.Y., 2020. Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents. *Pediatr. Infect. Dis. J.* 39 (8), e199–e200.
- Mazzoni, A., Salvati, L., Maggi, L., et al., 2020. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J. Clin. Investig.*
- Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J., HLH Across Speciality Collaboration, U., 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395 (10229), 1033–1034.
- Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M., Schneider, J., Brünink, S., Greuel, S., Lehmann, M., Hassan, O., Aschman, T., Schumann, E., Chua, R.L., Conrad, C., Eils, R., Stenzel, W., Windgassen, M., Rößler, L., Goebel, H.H., Gelderblom, H.R., Martin, H., Nitsche, A., Schulz-Schaeffer, W.J., Hakroush, S., Winkler, M.S., Tampe, B., Scheibe, F., Körtvelyessy, P., Reinhold, D., Siegmund, B., Kühl, A.A., Elezurtaj, S., Horst, D., Oesterhelweg, L., Tsokos, M., Ingold-Heppner, B., Stadelmann, C., Drosten, C., Corman, V.M., Radbruch, H., Heppner, F.L., 2021. Olfactory transnucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat. Neurosci.* 24 (2), 168–175.
- Doobay, M.F., Talman, L.S., Obr, T.D., Tian, X., Davissou, R.L., Lazartigues, E., 2007. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292.
- Miners, S., Kehoe, P.G., Love, S., 2020. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimer's Res. Ther.* 12 (1), 170.
- Miskowiak, K.W., Johnsen, S., Sattler, S.M., Nielsen, S., Kunalan, K., Rungby, J., Lapperre, T., Porsberg, C.M., 2021. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* 46, 39–48.
- Desforges, M., Le Coupanec, A., Dubeau, P., et al., 2019. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses* 12 (1).
- Li, Y.C., Bai, W.Z., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol.* 92.
- Heppburn, M., Mullaguri, N., George, P., et al., 2020. Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? *Neurocrit. Care* 34.
- Ghannam, M., Alshaer, Q., Al-Chalabi, M., et al., 2020. Neurological involvement of coronavirus disease 2019: a systematic review. *J. Neurol.*
- Nath, A., 2020. Neurologic complications of coronavirus infections. *Neurology* 94 (19), 809–810.
- neurology GPJJo. Neurological Manifestations of COVID-19: A Review of What We Know so far.** 2020.
- Novi, G., Rossi, T., Pedemonte, E., Saitta, L., Rolla, C., Roccatagliata, L., Inglese, M., Farinini, D., 2020. Acute disseminated encephalomyelitis after SARS-CoV-2. *Neurology. Neuroimmunol. Neuroinflamm.* 7 (5).
- Numbers, K., Broday, H., 2021. The effects of the COVID-19 pandemic on people with dementia. *Nat. Rev. Neurol.* 17 (2), 69–70.
- Alenina, N., Bader, M., 2019. ACE2 in brain physiology and pathophysiology: evidence from transgenic animal models. *Neurochem. Res.* 44, 1323–1329.
- Leite, C., Barbosa, A., Lucato, L.T., 2015. Viral diseases of the central nervous system. *Top. Magn. Reson. Imaging* 11, 44–54.
- Pezzini, A., Padovani, A., 2020. Lifting the mask on neurological manifestations of COVID-19. *Na. Rev. Neurol.* 16 (11), 636–644.
- Pilotto, A., Odolini, S., Masciocchi, S., Comelli, A., Volonghi, I., Gazzina, S., Nocivelli, S., Pezzini, A., Focà, E., Caruso, A., Leonardi, M., Pasolini, M.P., Gasparotti, R., Castelli, F., Ashton, N.J., Blennow, K., Zetterberg, H., Padovani, A., 2020. Steroid-responsive encephalitis in coronavirus disease 2019. *Ann. Neurol.* 88 (2), 423–427.
- Poyiadji, N., Shahin, G., Nourjain, D., Stone, M., Patel, S., Griffith, B., 2020. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology* 296 (2).
- Pun, B.T., Badenes, R., Heras La Calle, G., Orun, O.M., Chen, W., Raman, R., Simpson, B. K., Wilson-Linville, S., Hinojal Olmedillo, B., Vallejo de la Cueva, A., van der Jagt, M., Navarro Casado, R., Leal Sanchez, P., Orhun, G., Ferrer Gómez, C., Núñez Vázquez, K., Piñero Otero, P., Tazón, F.S., Gallego Curto, E., Caricato, A., Woien, H., Lacave, G., O'Neal HR, Jr, Peterson, S.J., Brummel, N.E., Girard, T.D., Ely, E.W., Pandharipande, P.P., COVID-Intensive Care International Study, G., 2021. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir. Med.* 9 (3), 239–250.
- Qin, Y., Wu, J., Chen, T., Li, J., Zhang, G., Wu, D., Zhou, Y., Zheng, N., Cai, A., Ning, Q., Manyande, A., Xu, F., Wang, J., Zhu, W., 2021. Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. *J. Clin. Investig.* 131 (8).
- Ye, Q., Wang, B., Mao, J., 2020. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J. Infect.* 80.
- Remsik, J., Wilcox, J.A., Babady, N.E., McMillen, T.A., Vachha, B.A., Halpern, N.A., Dhawan, V., Rosenblum, M., Jacobuzio-Donahue, C.A., Avila, E.K., Santomasso, B., Boire, A., 2021. Inflammatory leptomeningeal cytokines mediate COVID-19 neurologic symptoms in cancer patients. *Cancer Cell* 39 (2), 276–283, 276–283.e273.
- Rhea, E.M., Logsdon, A.F., Hansen, K.M., Williams, L.M., Reed, M.J., Baumann, K.K., Holden, S.J., Raber, J., Banks, W.A., Erickson, M.A., 2021. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. *Nat. Neurosci.* 24 (3), 368–378.
- van Riel, D., Verdijk, R., Kuiken, T.J.T., 2015. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J. Pathol.* 235 (2), 277–287.
- Romero-Duarte, Á., Rivera-Izquierdo, M., Guerrero-Fernández de Alba, I., Pérez-Contreras, M., Fernández-Martínez, N.F., Ruiz-Montero, R., Serrano-Ortiz, Á., González-Serna, R.O., Salcedo-Leal, I., Jiménez-Mejías, E., Cárdenas-Cruz, A., 2021. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med.* 19 (1), 129.

- Sankowski R., Mader S., Valdés-Ferrer S.J.F. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. 2015, 9: 28.
- Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A.V., Skriabine, S., Lu, P., Weizman, O.E., Liu, F., Dai, Y., Szigeti-Buck, K., Yasumoto, Y., Wang, G., Castaldi, C., Heltke, J., Ng, E., Wheeler, J., Alfajaro, M.M., Levavasseur, E., Fontes, B., Ravindra, N.G., Van Dijk, D., Mane, S., Gunel, M., Ring, A., Kazmi, S., Zhang, K., Wilen, C.B., Horvath, T.L., Plu, I., Haik, S., Thomas, J.L., Louvi, A., Farhadian, S.F., Huttner, A., Seilhean, D., Renier, N., Bilguvar, K., Iwasaki, A., 2021. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J. Exp. Med.* 218 (3).
- 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 (1).
- Oxley, T.J., Mocco, J., Majidi, S., et al., 2020. Large-vessel stroke as a presenting feature of Covid-19 in the Young. *New Engl. J. Med.* 382.
- Toscano, G., Palmerini, F., Ravaglia, S., Ruiz, L., Invernizzi, P., Cuzzoni, M.G., Franciotta, D., Baldanti, F., Daturi, R., Postorino, P., Cavallini, A., Micieli, G., 2020. Guillain-Barré syndrome associated with SARS-CoV-2. *New Engl. J. Med.* 382 (26), 2574–2576.
- Trigo, J., García-Azorín, D., Planchuelo-Gómez, Á., Martínez-Pías, E., Talavera, B., Hernández-Pérez, I., Valle-Peñacoba, G., Simón-Campo, P., de Lera, M., Chavarría-Miranda, A., López-Sanz, C., Gutiérrez-Sánchez, M., Martínez-Velasco, E., Pedraza, M., Sierra, Á., Gómez-Vicente, B., Arenillas, J.F., Guerrero, Á.L., 2020. Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study. *J. Headache Pain* 21 (1), 94.
- Wang, C., Fei, D., Li, X., Zhao, M., Yu, K., 2020. IL-6 may be a good biomarker for earlier detection of COVID-19 progression. *Intensive Care Med.* 46 (7), 1475–1476.
- Wang, F., Kream, R.M., Stefano, G.B., 2020. Long-term respiratory and neurological sequelae of COVID-19. *Med. Sci. Monitor: Int. Med. J. Exp. Clin. Res.* 26, 928996.
- Wang, Y., Wang, Y., Chen, Y., Qin, Q., 2020. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J. Med. Virol.* 92 (6), 568–576.
- Wang, Y., Wang, Y., Luo, W., et al., 2020. A comprehensive investigation of the mRNA and protein level of ACE2, the putative receptor of SARS-CoV-2, in human tissues and blood cells. *Int. J. Med. Sci.* 17.
- von Weyhern, C.H., Kaufmann, I., Neff, F., Kremer, M., 2020. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet* 395.
- Widmann, C.N., Heneka, M.T., 2014. Long-term cerebral consequences of sepsis. *Lancet Neurol.* 13 (6), 630–636.
- Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B. S., McLellan, J.S., 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367 (6483), 1260–1263.
- Wu, Z., McGoogan, J.J.J. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. 2020.
- Xu, J., Lazartigues, E.J.C., neurobiology m. Expression of ACE2 in Human Neurons Supports the Neuro-Invasive Potential of COVID-19 Virus. 2020.
- Jin, X., Lian, J.S., Hu, J.H., 2020. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms, 69 (6), 1002–1009.
- Yates, D.A., 2021. CNS gateway for SARS-CoV-2. *Nat. Rev. Neurosci.* 22 (2), 74–75.
- Huang, Y.H., Jiang, D., Huang, J.T., 2020. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav. Immun.* 87.
- Li, Y., Shen, X., Yang, R.F., 2003. Identification of an epitope of SARS-coronavirus nucleocapsid protein. *Cell Res.* 13, 141–145.
- Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., Yang, C., 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav. Immun.*
- Zhang, X., Tan, Y., Ling, Y., et al., 2020. Viral and host factors related to the clinical outcome of COVID-19. *Nature* 583, 437–440.
- Zhang, Y., Xiao, M., Zhang, S., et al., 2020. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *New Eng. J. Med.* 382.
- Zheng, J., Wong, L.R., Li, K., Verma, A.K., Ortiz, M.E., Wohlford-Lenane, C., Leidinger, M.R., Knudson, C.M., Meyerholz, D.K., McCray PB, Jr, Perlman, S., 2021. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. *Nature* 589 (7843), 603–607.
- Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. 2020, 395(10229): 1054–1062.
- Zubair, A.S., McAlpine, L.S., Gardin, T., Farhadian, S., Kuruvilla, D.E., Spudich, S., 2020. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* 77, 1018–1027.