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Review

Central nervous system as a target of novel coronavirus infections: Potential routes of entry and pathogenic mechanisms

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Since the COVID-19 pandemic started in December 2019, there have been several reports of patients succumbing to neurological complications. Early reports were suggestive of a possibility, while by early 2020 it was clearly evident that although SARS-CoV-2 primarily attacks the respiratory system, the brain is one of the most affected organs post-recovery. Although it may be premature to comment on the long-term effects of COVID-19 in brain, some reliable predictions can be made based on the data currently available. Further, exploring the CNS connections of SARS-CoV-2 is of keen interest for neuroscience researchers. As soon as the virus enters the nasal region, it is exposed to the olfactory nervous system which is interlinked with the visual system, and hence we explore the mechanism of entry of this virus into CNS, including brain, olfactory and retinal nervous systems. In this review, we have thoroughly reviewed reports about both SARS-CoV-1 and SARS-CoV-2 with respect to their ability to breach the blood-brain and blood-retinal barriers. We have compiled different neurological conditions resulting from COVID-19 and looked into viral infections related to COVID-19 to understand how the virus may gain control of the olfactory and visual systems. Once the dust settles on the pandemic, it would be interesting to explore the extent of viral infection in the CNS. The long-term effects of this virus in the CNS are not yet known, and several scientific research papers evolving in this field will throw light on the same.

Keywords. Coronavirus; COVID-19; neurological manifestations; systematic review; viral infection

1. Introduction

Coronaviruses belong to the family Coronaviridae, and the name is derived from the Latin word *corona*, meaning crown. This refers to the distinctive structure of the virus envelope, containing projections that give it the appearance of a crown. Coronaviruses (CoVs) infecting humans can cause a wide range of respiratory, hepatic, gastrointestinal and neurological diseases, and have been identified in two genera: alpha- and beta-coronaviruses. Among the beta CoVs, Severe Acute Respiratory Syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV) emerged in the early 2000s in humans.

The genome of the novel coronavirus that was reported in Wuhan, China, in December 2019, taxonomically designated SARS-CoV-2 is a single-stranded positive-sense RNA, about 30 kb in length, and is among the largest-known RNA viruses. The disease caused by SARS-CoV-2, officially named Coronavirus Disease-2019 (COVID-19) by the World Health Organization (WHO), and declared a public health emergency of international concern by late January 2020, leads to lower respiratory distress with a global mortality rate of 5–6% on average. Most infected persons have mild respiratory symptoms; however, some

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develop severe respiratory distress and death occurs due to multiple organ complications (table 1).

2. Neurological manifestations of SARS-CoV-2 infection

The COVID-19 pandemic quickly spread to almost all the continents last year, but we have just begun to understand the complexities and manifestations of this syndrome. Although there is still dearth of available medical literature detailing the neurologic manifestations in patients suffering from SARS-CoV-2 infection, crucial information was reported from patients undergoing treatment in China and elsewhere in the world (Ellul *et al.* 2020). It was a common notion that Coronaviruses do not impact the brain or nervous system, but time and again since the SARS outbreak this perception has been proven wrong (Matías-Guiu *et al.* 2020a). Out of the total number of SARS-CoV-2 patients requiring hospitalization, 10–20% require Intensive care unit (ICU) admission and subsequently required mechanical ventilation support (Borges do Nascimento *et al.* 2020). Although the reported clinical symptoms of patients suffering from the viral infection include fever, dry cough and fatigue, there is increasing evidence of neurological involvement in some late-stage cases (Cascella *et al.* 2020; Aaroe *et al.* 2020). However, little can be done after a patient reaches extant neurological damage. This makes it necessary to detect the neuronal damage in early stages of the disease. In one of the reported cases during the SARS epidemic, the SARS-CoV virus was isolated from the brain of a patient exhibiting neurological deficit after 28 days of infection (Baig 2020). Similar results were observed from brain autopsies of COVID-19 patients where the brain tissue was edematous with degenerated neurons (Matías-Guiu *et al.* 2020b). Studies from the SARS outbreak have demonstrated that SARS-CoV can target the CNS and the brain. The immunohistochemistry studies performed on the brain autopsies of SARS patients demonstrate edema with neuronal degeneration and electron micrographs confirmed viral infection of the neurons. This raises the possibility of increased number of patients with neurological manifestations during the COVID-19 pandemic. A retrospective study from the frontline in Wuhan where the pandemic began revealed that out of 214 patients studied, 36.4% displayed various neurologic manifestations involving CNS, PNS, and skeletal muscles (Mao *et al.* 2020a). CNS-based neurological manifestations included dizziness, headache, altered consciousness levels such as stupor, coma and delirium, ataxia, acute cerebrovascular disease and seizure. On the other hand, PNS-based neurological manifestations included taste, smell and vision impairment and nerve pain (Mao *et al.* 2020a). In another unique study of its kind, a Chinese male patient infected with SARS-CoV-2 and having neurological manifestations was found to have the virus in cerebrospinal fluid (CSF) (Moriguchi *et al.* 2020). Although the lungs are the most affected organ in SARS-CoV-2 infection due to the abundance of ACE-2 in alveolar cells, there is an increasing body of evidence that this virus affects the brain to a great extent that it will leave severe long-lasting impact. It is believed that the neuro-invasive potential of the virus could be responsible for the abnormal respiratory response. Indeed, it was shown that coronavirus could reach the brainstem through a connected synapse (Iroegbu *et al.* 2020). The brain's medulla oblongata and lower brain stem control the respiratory reflex, and therefore impaired cough and gag reflex may be an early sign of neurologic manifestation during the disease. Additionally, there are reports of increasing number of patients showing intracerebral haemorrhages (Iroegbu *et al.* 2020). It is yet to be demonstrated whether these hemorrhages are a result of uncontrolled hypertension due to interaction of SARS-CoV-2 with ACE-2 receptor. Further studies will help determine if hypertensive encephalopathy could be considered an early sign of impending neurological manifestations in COVID-19 patients. Therefore, it is critical to study the underlying mechanisms of neuronal damage in SARS-CoV-2 infection.

3. Pathogenic strategy of SARS-CoV-2 and CNS tropism

The spike protein (S) of the novel coronavirus SARS-CoV-2 exhibits 73–76% receptor binding domain similarity with that of the earlier SARS-CoV. This high level of similarity indicates that SARS-CoV-2 potentially binds to host cell membrane through the same host receptors as SARS-CoV, namely the angiotensin-converting enzyme 2 (ACE2). Moreover, the ACE2 binding affinity of human host cells with SARS-CoV-2 spike protein is revealed to be 10–20 fold higher than SARS-CoV (Wrapp *et al.* 2020). A serine protease TMPRSS2 may be required for S protein priming. Comparison of the SARS-CoV and SARS-CoV-2 receptor-binding-motifs shows no evidence of deletions or insertions, confirming the role of ACE2 and TMPRSS2 in COVID-19 (Wan *et al.* 2020; Hoffmann

Table 1. Manifestations of COVID-19 beyond respiratory distress

Symptoms	Publications
Viral encephalitis	A first case of meningitis/encephalitis associated with SARS-Coronavirus-2 (Moriguchi et al. 2020).
Infectious toxic encephalopathy or acute toxic encephalitis and edema in brain tissues of COVID-19 patients	Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study (Mao *et al.* 2020a).
Acute cerebrovascular disease	Nervous system involvement after infection with COVID-19 and other coronaviruses (Wu *et al.* 2020b).
Headache, dizziness, seizures, impaired consciousness	Neurological manifestation of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study (Mao *et al.* 2020a).
Acute ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage	1. Acute cerebrovascular disease following COVID-19: A single center, retrospective, observational study (Li *et al.* 2020a). 2. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke (Al Saiegh *et al.* 2020). 3. COVID-19 presenting as stroke (Avula *et al.* 2020).
Guillain-Barre syndrome	Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? (Zhao *et al.* 2020b).
Acute respiratory distress	The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients (Li *et al.* 2020b).
Conjunctivitis Ocular abnormalities	1. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A Review of coronaviruses and ocular implications in humans and animals (Seah and Agrawal 2020). 2. Characteristics of ocular finding of patients with coronavirus disease 2019 (COVID-19) in Hubei province, China (Wu *et al.* 2020a). 3. Spreading SARS-CoV-2 through ocular fluids (CEBM) 4. Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: A cross-sectional study (Chen *et al.* 2020a). 5. Ocular manifestations of a hospitalized patient with confirmed 2019 novel coronavirus disease (Chen *et al.* 2020b). 6. Haemorrhagic conjunctivitis with pseudomembranous related to SARS-CoV-2 (Navel *et al.* 2020).
Loss of olfaction	Smell and taste dysfunction in patients with COVID-19 (Xydakis *et al.* 2020).
Skeletal muscle injury	Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study (Mao *et al.* 2020a).

et al. 2020). An over-expression of TMPRSS2 and ACE2 receptors was observed in SARS-CoV-infected tissues (Gupta *et al.* 2020b; Zhang *et al.* 2020). Exploring the expression patterns of these receptors in infected tissues of COVID-19 patients may yield similar results.

ACE2 receptor in humans is expressed in a variety of organs such as lungs, intestine, brain, heart, liver, lymphoma cells, capillary endothelium, and testis (Palasca *et al.* 2018). All these organs should therefore be considered as potential targets of COVID-19. The symptoms of COVID-19 indicate that lungs, brain, and intestines may be affected. ACE2 expression in lungs is mainly in the alveolar type 2 (AT2) cells, followed by low level expression in AT1 and fibroblasts cells. AT2 cells were found to be the most affected during the SARS-CoV infection, and this cell type may well be the main target for COVID-19. Any change in expression level of ACE2 in AT2 can thus affect the severity of disease progression (Zhang *et al.* 2020).

Most β-coronaviruses that infect humans, including SARS-CoV and MERS have demonstrated neuroinvasive potential. A SARS-CoV-2 isolate from Germany was demonstrated to infect neurons in 3D human brain organoids, and was associated with Tau abnormalities and neuronal cell death (Ramani *et al.* 2020). In human SARS-CoV-2 infection, fatality appears to be due to widespread dysregulation of homeostasis caused by lung, kidney, cardiac and circulatory damage. However, cerebral damage may complicate SARS-CoV-2 infections. Another study found that among SARS-CoV-2 infected patients in Wuhan, 36.4% demonstrated neurological manifestations such as headache, dizziness and epilepsy (Mao *et al.* 2020a). The virus has also been detected in the cerebrospinal fluid of some patients (Moriguchi *et al.* 2020). A case study published on 31 March 2020 reported a COVID-19 patient developing acute haemorrhagic necrotizing encephalopathy (Poyiadji *et al.* 2020). Although the association of cerebral damage to SARS-CoV-2 infection has not been confirmed yet, this type of rare encephalopathy has been previously linked to other viral infections such as influenza (figure 1).

SARS-CoV-2 may cause neurological damage by a variety of mechanisms. They may enter the CNS either directly through the olfactory nerve, or through the systemic circulation by breaching the blood-brain and blood-retinal barriers. After gaining entry into the CNS, these viruses may lead to neuronal damage as a result of encephalitis (inflammation in the brain), encephalopathy (cerebral oedema), or cerebrovascular events (ischaemic injury due to cytokine cascades).The ACE2 receptor is present on glia as well as neurons. Hence, SARS-CoV-2 can potentially bind to ACE2 on glial cells in the CNS via spike proteins.

4. SARS CoV- 2 and the blood-brain barrier

The BBB is made up of highly specialized cells such as vascular endothelial cells, pericytes, astrocytes, microglia and neurons which act in concert to prevent the entry of bacteria, viruses, immune cells and soluble molecules into the central nervous system (CNS) (Keaney and Campbell 2015). If viruses succeed in crossing this barrier and infect the CNS, the BBB can open in a regulated manner to allow leukocyte transmigration into the CNS, so that virus-infected cells, dead cells and debris can be cleared (Reynolds and Mahajan 2021). Recent studies show that significant upregulation of inflammatory cytokines such as TNF-α, IL-6, IL-10, and IL-23 could occur in COVID-19 patients and that such a 'cytokine storm' could be a crucial factor in disrupting the BBB (Reynolds and Mahajan 2021; Alquisiras-Burgos *et al.* 2021).

Neurotropic viruses that cause encephalopathy or encephalitis contribute significantly to global mortality and morbidity. These infections can lead to mild cognitive impairment and memory loss, and in some cases may even result in permanent CNS damage and death (Wu *et al.* 2020b). However, neuroinvasion occurs only in a small percentage of persons infected with neurotropic viruses. It is believed that host-pathogen interactions at the BBB may play a role in preventing these viruses from gaining access to glia and neurons of the CNS (Wu *et al.* 2020b).

SARS-CoV-2 spike protein has high affinity for the ACE2 protein which is expressed on the capillary endothelial cells, among other cell types. The virus may infect the capillary endothelium, and budding of virus particles from endothelial cells may damage the BBB leading to subsequent entry of the virus from systemic circulation into the brain. Indeed, it was recently reported that S1 protein of SARS-CoV-2 crosses the BBB in mice (Rhea *et al.* 2021).

5. SARS CoV-2 and the olfactory route

ACE2 receptors in the brain are expressed in neurons and glia in different regions like the olfactory bulb, cortex, hippocampus and major nuclei including nucleus tractus solitaries (NTS), rostral ventrolateral medulla (RVLM) and paraventricular nucleus. It is also highly expressed in brain regions involved in cardiovascular regulation (Wu *et al.* 2020b). Experiments in mouse models expressing human ACE2 receptors and subsequent exposure to SARS-CoV suggests that the olfactory pathway may be a means of virus entry to the brain, and the olfactory bulb may be the primary point of infection. This model also suggests a transneuronal spread of coronaviruses from the olfactory bulb to the rest of the brain. In the mice that survived infection, loss of neurons was detected in infected brain regions (Netland *et al.* 2008).

An increase in clinical results showing loss of olfaction as an early symptom of COVID-19 patients indicates that the infection may proceed through the olfactory pathway (Eliezer *et al.* 2020).The olfactory ensheathing glial cells (OEC), with high ACE2 expression or the olfactory receptors neurons (ORN) with mosaic expression of TMPRSS2, may be the first sites of infection in this pathway. Both these cell types are present in the olfactory epithelium (OE), making

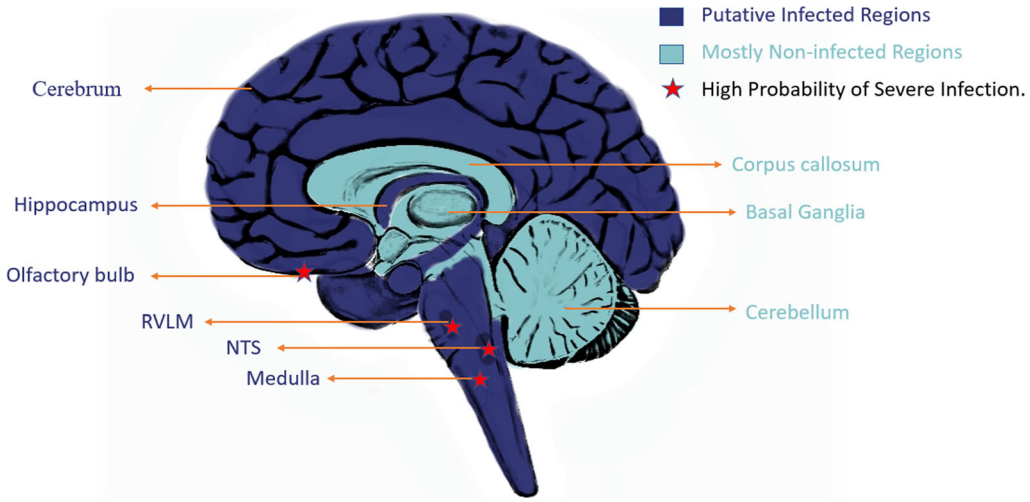

Figure 1. Most commonly reported SARS-CoV-2 infected regions of the brain, marked and colour-coded based on the probability of infection and severity. Regions of the brain that have a high probability of being severely infected by SARS-CoV-2 include olfactory bulb, medulla, nucleus tractus solitaries (NTS) and rostral ventrolateral medulla (RVLM), indicated by red asterisk. Hippocampus and cerebrum are other regions likely to be infected by the virus (dark blue), while cerebellum, basal ganglia and corpus callosum (light blue) are not likely to be infected.

the OE a potential viral reservoir (Butowt and Bilinska 2020). Most β-coronaviruses such as MERS and SARS show a similar mechanism of infection, based on which a plausible mechanism can be extrapolated for SARS-CoV-2 (Eliezer *et al.* 2020):The viruses bud from the endoplasmic reticulum, pass through Golgi intermediate compartments, and assemble as vesicles. The virions are then released outside the cell through exocytosis, and will be taken up as lysosome-like structures by satellite cells or neurons. Neurons may spread the virus by three means:

Smooth-surfaced vesicle secretion at perikaryal specializations of neurons infecting satellite cells
Membrane-embedded spike protein secretions at axon end infecting neurons
Free particles diffusion infecting neurons and glial cells

In this manner, the virus can enter cells which do not even express the appropriate receptors. (Dubé *et al.* 2018; Li *et al.* 2020).

A study published in 2008 describes SARS-CoV infection of mice transgenic for human ACE2 (hACE2), in which the virus enters the brain primarily through the olfactory bulb. This resulted in dysfunction and death of neurons in cardiorespiratory centres in the medulla. Interestingly, very little infection was detected in the lungs, and extensive neuronal infection appeared to be the main cause of death (Netland *et al.* 2008).

Recent literature suggests that nasal epithelium may be a major source of viral RNA after COVID-19 infection, based on experiments on macaques, cats and ferrets. Moreover, the paper reveals the ability of SARS-CoV-2-positive cells to transverse the olfactory epithelium, and suggests the sustentacular cells as primary targets for infection (Cooper *et al.* 2020). The SARS-CoV-2 infection may subsequently spread to the brain, either through regions possessing a first-order connection with the olfactory bulb, or through the CSF. The infection may further escalate to other brain regions depending on the expression levels of the ACE-2 receptor (Wu *et al.* 2020a). Loss of olfaction is an early symptom, and this implies that the olfactory bulb may be the primary affected area in the brain (Baig *et al.* 2020).

Degeneration of olfactory bulb neurons has been observed in patients with persistant COVID-19 olfactory dysfunction (Kandemirli *et al.* 2021). The loss of olfaction may be due to the loss of neurons in the olfactory region (Gupta *et al.* 2020b). The NTS and neurons in medulla control the involuntary function of the lungs, and the presence of ACE2 receptors in this region makes it vulnerable to COVID-19 infection. Infection and subsequent death of neurons in NTS may lead to the failure of lung movement, leading to difficulty in breathing- a major symptom of COVID-19 (Li *et al.* 2020).

6. SARS CoV-2 and the blood-retinal barrier

Five types of neurons are present in the retina-ganglion cells, amacrine cells, bipolar cells, horizontal cells and photoreceptors (rods and cones). Light is absorbed by

photoreceptor cells which transfer the signal to bipolar cells, and further to ganglion cells. Retinal ganglion cells convey these signals to the CNS through the optic nerve. The blood-retinal barrier (BRB) protects the retina, and helps maintain a balanced retinal environment for optimal visual function. The BRB is essentially an extension of the blood-brain barrier (BBB) (Purves *et al.* 2001; Cunha-Vaz *et al.* 2011).

The BRB is divided into two modules: inner BRB (iBRB) and outer BRB (oBRB). The BRB is a barrier which regulates the movement of molecules and fluids into the retina. It also prevents leakage of harmful agents and macromolecules into the retina. The iBRB is established by tight junctions (TJs) between the retinal endothelial cells underlying retinal capillaries. The oBRB is established by the TJs between neighbouring retinal pigment epithelial (RPE) cells, and serves to separate the choroidal system from the sensory retina. The oBRB protects the neuroretina from blood-borne pathogens. Alterations in the BRB play a very important role in the development of retinal diseases. The two most common retinal diseases are age-related macular degeneration (AMD) and diabetic retinopathy (DR). These two diseases are caused by changes in BRB (Purves *et al.* 2001).

Several factors cause inflammation in the retina, leading to disease. Bacteria, viruses, parasites and fungi are capable of breaching the BRB and infecting retina. This may cause inflammation and ocular infections like conjunctivitis, endophthalmitis, and keratitis which are most commonly caused by bacteria and viruses (Singh *et al.* 2017; Belyhun *et al.* 2018).

RNA viruses such as Dengue virus, Chikungunya and Zika virus (ZIKV) are known to have ocular manifestations. Previous studies have demonstrated that direct inoculation of ZIKV in mouse eye makes the BRB, RPE layer and retinal endothelium highly permeable, and also induces cell death. In adults, this virus causes retinal edema and retinal hemorrhages (Singh *et al.* 2017; Donoso Mantke *et al.* 2018; Manangeeswaran *et al.* 2018). Dengue virus also infects the retina and the cells lining the BRB, causing dengue retinopathy, macular edema and retinal vasculopathy. The mechanism of dengue retinopathy is poorly understood, but dengue patients show loss of RPE cells and decrease in the integrity of epithelial barrier (Donoso Mantke *et al.* 2018). The murine coronavirus, mouse hepatitis virus (MHV) causes a biphasic retinal disease in mice. The viral RNA of MHV persists within the retina for a long time and causes retinal degeneration. In one study, the viral RNA was detected in the inner and outer layer of retina, and also in ganglion cell layer within the retina, inducing apoptosis and leading to murine retinopathy (Komurasaki *et al.* 1996; Wang *et al.* 2000).

There are several types of CoV that are known to infect humans and animals. These CoV mainly affect the respiratory tract, but they may also affect ocular tissue. Patients infected with SARS-CoV-2 show ocular complications like conjunctivitis (Seah and Agrawal 2020a). Tears and conjunctival secretion from SARS-CoV-2 patients have been shown to contain viral RNA, and this viral RNA can further infect healthy persons (Ferner *et al.*). A recent report shows that out of 31 SARS-CoV-2-infected patients, 9 were severely affected, and the conjunctival secretion and tears samples tested positive for the virus by RT-PCR (Ferner *et al.*; Seah and Agrawal 2020b; Sun *et al.* 2020b). The summary of probable Coronavirus interactions and associated abnormalities in CNS and PNS is listed in table 2 and graphically represented in figure 2.

7. Clinical management of COVID-19 neurological manifestations

The incidence and complete clinical manifestations of COVID-19 effects on CNS is still not fully understood. Learnings from global scientific and clinical studies suggest that SARS-CoV-2 can invade the nervous system. However, when studied in totality, clinically-relevant direct CNS involvement has not been established. As per published reports, neurologic manifestations appear to be present in 36.4% to 69% of all COVID-19 patients requiring hospitalization (Mao *et al.* 2020b; Carod Artal 2020).

The manifestations observed in clinical settings included delirium, anosmia or abnormalities in smell and taste observed in almost all the patents suffering from COVID-19, headache in almost 70% of hospitalized patients, signs of corticospinal tract in 67% of patients, dizziness in 17% of patients and stroke in 5% of patients requiring hospitalization (Carod-Artal 2020; Helms *et al.* 2020; Mao *et al.* 2020a; Aaroe *et al.* 2020). Although SARS-CoV-2 may not infect CNS directly, the virus may increase risk of neurological disease (Xu *et al.* 2020a). The pathophysiology of these neurological manifestations is currently unknown, but possible mechanisms include hypoxia-mediated injuries (Kotfis *et al.* 2020; Asadi-Pooya 2020), systemic proinflammatory conditions (Nie *et al.* 2020), and possible blood-brain barrier disruption subsequent to SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) (Cipriano *et al.* 2020).

SARS-CoV-2-related neurological manifestations can be broadly categorized into two different types based on

Table 2. CNS and PNS abnormalities observed in COVID-19 patients

Symptoms	Publications
Structured delusions mixed with confusional features	Psychotic symptoms in COVID-19 patients. A retrospective descriptive study (Parra *et al.* 2020)
Hallucination in different forms of modality, delusion, disorganized speech, and grossly disorganized or catatonic behaviors	Available evidence and ongoing hypothesis on corona virus (COVID-19) and psychosis: Is corona virus and psychosis related? A narrative review (Tariku and Hajure 2020)
Psychosis	COVID-19-associated brief psychotic disorder (Smith *et al.* 2020)
Disruption to micro-structural and functional brain integrity in the recovery stages of COVID-19. (higher bilateral gray matter volumes and decline in mean, axial and radial diffusivity)	Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3-month follow-up study (Lu *et al.* 2020)
Sensory loss, and worsening cognitive impairment	A case of COVID-19 with memory impairment and delayed presentation as stroke (Garg *et al.* 2020)
Rhombencephalitis (persisting oscillopsia and ataxia was also reported)	Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection (Wong *et al.* 2020)
Acute Hemorrhagic Necrotizing Encephalopathy	Neurological complications of coronavirus disease (COVID-19): encephalopathy (Poyiadji *et al.* 2020)
Cerebral venous thrombosis	First case of Covid-19 presented with cerebral venous thrombosis: A rare and dreaded case (Hemasian and Ansari 2020)
Fulminant myocarditis	Fulminant myocarditis due to COVID-19 (Bernal-Torres *et al.* 2020)
Heart failure	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study (Zhou *et al.* 2020)
Cardiac arrests and arrhythmias	COVID-19 and cardiac arrhythmias (Bhatla *et al.* 2020)
Higher rate of preterm birth, preeclampsia, cesarean, and perinatal death	Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis (Di Mascio *et al.* 2020)
Hyperfibrinolysis associated with plasmin elevation	Elevated Plasmin (ogen) as a Common Risk Factor for COVID-19 Susceptibility (Ji *et al.* 2020)

their impact on the nervous system: Manifestations arising as a result of direct invasion of SARS-CoV-2 virus on the nervous system include anosmia, encephalitis and myelitis. The other type of manifestations include those occurring as a result of SARS-CoV-2 infection in other systems. This subset includes clinical manifestations such as stroke, seizures and status epilepticus, altered mental status (AMS) including delirium, headache and neuromuscular disorders.

7.1 *Anosmia*

Acute loss of smell (anosmia) and taste (ageusia) are early or initial symptoms post SARS-CoV-2 infection (Tong *et al.* 2020). A study including 2 million participants identified smell and taste as the strong predictors of COVID-19 (Menni *et al.* 2020). Almost all COVID-19 positive patients report anosmia or ageusia or both, either at onset of disease or during the early stages of disease progression (Kaye *et al.* 2020; Sayin *et al.* 2020). Anosmia is reported in patients without any symptoms of nasal congestion or rhinorrhea, indicating possible local inflammation. Infections of the upper respiratory tract are thought to be responsible for sudden acute onset of anosmia or ageusia in COVID-19 patients (Hummel *et al.* 2011; Giacomelli *et al.* 2020).

In a mouse model, the SARS-CoV virus penetrates through the olfactory bulb transneuronally resulting in

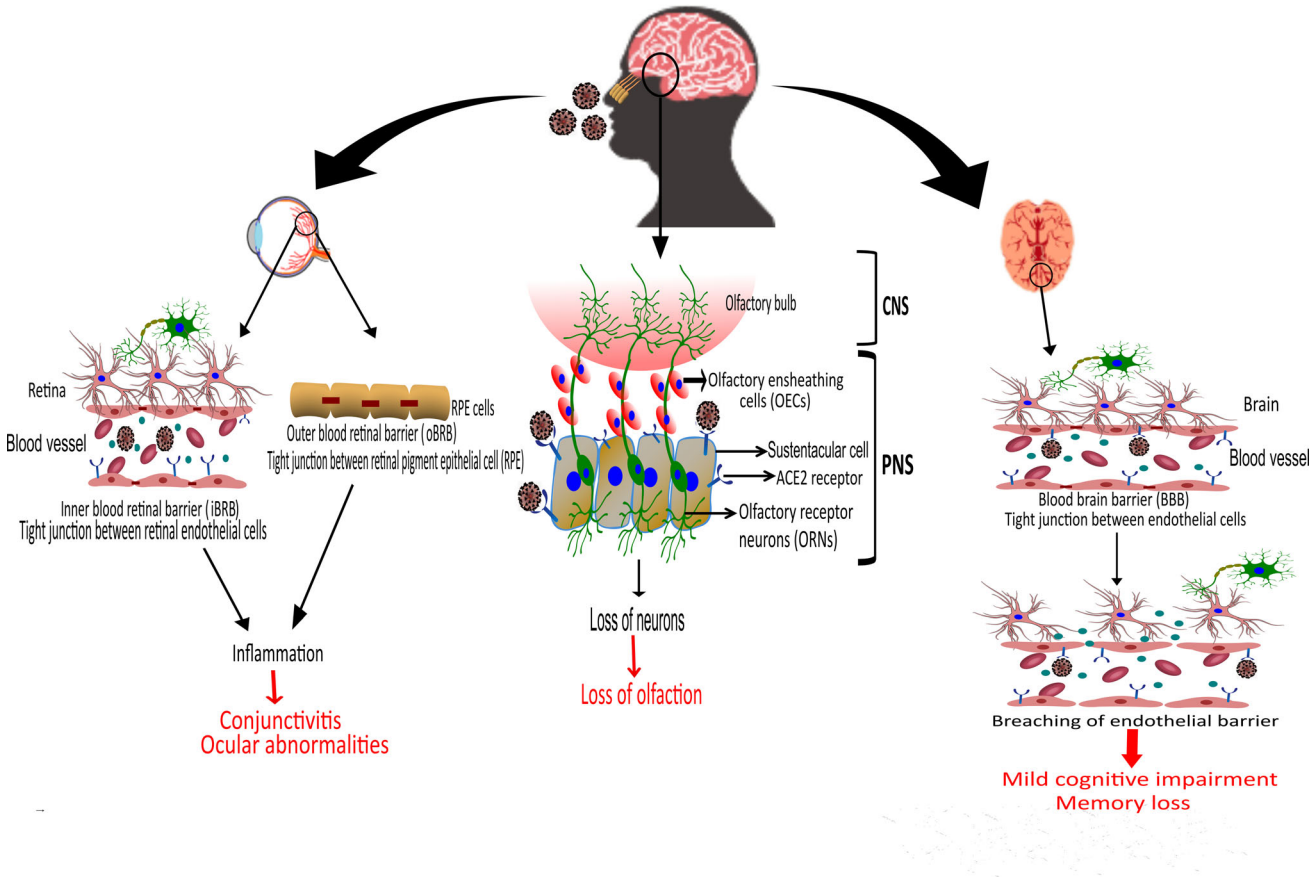

Figure 2. Schematic of probable Coronavirus interactions and associated abnormalities in CNS and PNS. SARS-CoV-2 interacts with ACE2 receptors which are expressed by retinal pigment epithelial cells. This binding may affect the cell lining of BRB and cause inflammation in retina, resulting in conjunctivitis and other ocular abnormalities (left). The virus may also interact with sustentacular cells through ACE2 receptors in the olfactory system and lead to loss of olfaction (center). In the brain, the virus may attach to endothelial cells in BBB that express ACE2 receptors, and impair the endothelial barrier thereby gaining access to brain regions which may further cause cognitive impairment and memory loss (right).

rapid spread of the virus to connected neuronal areas (van Riel *et al.* 2015). The virus may inflict damage to the olfactory nerve during invasion and multiplication, thereby resulting in acute anosmia in almost all the patients studied during early stages of the disease progression (Perlman and McCray 2013; Politi *et al.* 2020). Associated ageusia in some cases might be a secondary manifestation of olfactory dysfunction. Moreover, ACE-2 receptor- the main host cell surface receptor facilitating the virus binding and entry to host cell, is widely expressed on the epithelial cells of the oral mucosa, and damage to mucosal epithelium may be responsible of ageusia in early stages of COVID-19 disease (Xu *et al.* 2020c).The neuroinvasive nature of COVID-19 is slowly emerging through recent studies demonstrating the presence of ACE2 in the mitral cells of olfactory bulb, olfactory sensory neurons (OSN) nuclei and cortical neurons in human brain organoids (Cooper *et al.* 2020). However, imaging of the olfactory system in COVID-19 patients showed normal tissue or only focal inflammation (Lechien *et al.* 2020a). Inflammatory intermediates may lower the expression of the olfactory receptors, and this may explain the pathophysiology underlying observed anosmia in COVID-19 patients.

Among COVID-19 patients, approximately 66–80% display anosmia, but demonstrate spontaneous improvement and reach a complete resolution of this symptom within 7–10 days from the clinical onset of disease (Vaira *et al.* 2020; Yan *et al.* 2020; Hopkins *et al.* 2020; Lechien *et al.* 2020b). Use of corticosteroids to treat anosmia are contraindicated since most subjects recover from the condition without clinical intervention (Lee and Chong 2020).

7.2 *Encephalitis and myelitis*

Some studies describe SARS-COV-2 patients with impaired consciousness also presenting with acute

encephalitis. Several medical centres around the globe are reporting brain and CSF abnormalities (Carod-Artal 2020; De Felice *et al.* 2020; Huang *et al.* 2020; Bernard-Valnet *et al.* 2020; Gatto *et al.* 2020). Brain abnormalities were found in 37-62% of patients displaying neurologic symptoms and requiring MRI-based imaging. In a study on 13 encephalopathy patients with unclear etiology, 8 (62%) had leptomenengial enhancement (Helms *et al.* 2020). Out of this group, frontotemporal hypoperfusion was observed in all the 11 patients who underwent perfusion imaging. In another study, out of 27 patients admitted to ICU with neurologic symptoms, 37% demonstrated cortical abnormalities including 7 patients showing cortical diffusion restriction, 5 patients with subtle leptomeningeal enhancement and 3 patients with either subcortical or deep white matter signal abnormalities (Kandemirli *et al.* 2020).

Recent reports point to the fact that SARS-CoV-2 may also have neurotropic effects, with multiple COVID-19 patients presenting neurological symptoms along with common respiratory symptoms (Mao *et al.* 2020a). In a case study from Japan, SARS-CoV-2 RNA was detected in CSF of a patient suffering from clinically defined meningoencephalitis (Moriguchi *et al.* 2020). In another case study, a patient with clinically proven SARS-CoV-2 infection was CSF-negative for bacteria, herpes simplex virus type 1 and 2, varicella zoster virus, and West Nile virus. However, hemorrhagic ring enhancing lesions a characteristic of acute necrotizing encephalitis were observed in the bilateral thalami, medial temporal lobes and sub-insular regions (Poyiadji *et al.* 2020). Case reports such as these may have led to the popular belief that SARS-CoV-2 causes acute necrotizing encephalitis due to a 'cytokine storm' and that the virus need not directly infect the brain or CSF to cause these neurologic manifestations (Savarin and Bergmann 2018; Sun *et al.* 2020a; Balloy *et al.* 2020).

In terms of management of encephalitis, screening is first carried out to look for clinical features such as headache, nuchal rigidity, photophobia and altered conscious levels. Subsequently, CT/MRI-based imaging is performed to diagnose structural etiologies or vessel occlusion. In case of acute encephalitis, lumbar puncture is advised and the CSF is screened for presence of virus including SARS-CoV-2 (Tsivgoulis *et al.* 2020; Filatov *et al.* 2020; Poyiadji *et al.* 2020; Haddad *et al.* 2020). As a clinical management strategy, patients with suspected encephalopathy are treated with anti-infectives such as Ceftriaxone, Vancomycin and Acyclovir. These can be discontinued in lieu of specific treatment once the viral or bacterial processes are cleared during the clinical work-up mentioned above (McLaren *et al.* 2020; Murphy and Pardo 2020; Francis and Parsh 2020; Chong *et al.* 2020). In case of patients with acute necrotizing encephalitis along with unusual IL-6 elevation, Tocilizumab was found to demonstrate favorable clinical outcomes (Bilbul *et al.* 2020; Toniati *et al.* 2020).

7.3 *Cerebrovascular disease and stroke*

COVID-19 patients suffering from cerebrovascular disease are vulnerable to stroke as a result of a systemic inflammatory and prothrombotic state (Vonck *et al.* 2020). In some estimates, 4–5% of SARS-CoV-2-infected patients may suffer from stroke (Zhao *et al.* 2020; Tejada Meza *et al.* 2020; Morassi *et al.* 2020). Among such cases, ischaemic stroke is more prevalent than intracerebral hemorrhage or cerebral venous sinus thrombosis. Associated factors include co-morbidities like hypertension, diabetes or prior cerebrovascular disease (Moshayedi *et al.* 2020). Biochemical factors like elevated C-reactive protein and elevated D-dimer also result in stroke among patients suffering from severe SARS-CoV-2 infection (Yaghi *et al.* 2020; Tsushima *et al.* 2020; Xu *et al.* 2020b; Sato *et al.* 2020; Reddy *et al.* 2020).

The exact pathophysiology of stroke is still not clearly understood. But some conclusions can be drawn with respect to the association of cerebrovascular disease with the onset of COVID-19 infection. As mentioned earlier, studies have suggested that SARS-CoV-2 can exploit axonal transport to infect the brain via the cribriform plate and olfactory bulb (Tsivgoulis *et al.* 2020; Ellul *et al.* 2020). It has been clearly demonstrated that SARS-CoV-2 virus internalization is dependent on expression of ACE-2 on the cell surface. SARS-CoV-2 induces a down-regulation of ACE-2, which is predominantly expressed in cells, and tissues of the respiratory system, gastrointestinal tract and brain. This down-regulation of ACE-2 results in overactivation of Renin Angiotensin System (RAS) and simultaneous down-regulation of downstream alternative RAS signaling in the brain (Helms *et al.* 2020; Montalvan *et al.* 2020). Concomitant vasodilation, neuro-inflammation and thrombogenesis may lead to stroke in the brain during SARS-CoV-2 infection (Serrano-Castro *et al.* 2020).

As a clinical management strategy, tissue Plasminogen Activator (tPA) is administered intravenously for stroke resulting from SARS-CoV-2 infection (Hess and

Fagan 2010). In tPA-naïve patients with high risk of bleeding, Aspirin is administered as a part of anti-coagulative therapy. Also, high-intensity statins like Atorvastatin can be administered to stabilize the patient (Tuttolomondo *et al.* 2016; Zhang *et al.* 2019; Amarenco *et al.* 2019). Finally, if clinically appropriate, treatment of deep vein thrombosis can be considered (Ha *et al.* 2020).

7.4 *Altered mental status and delirium*

Delirium is one of the most common neurologic symptoms observed in COVID-19 patients (Kotfis *et al.* 2020; Beach *et al.* 2020). Moreover, hyperactive delirium characterized by waxing and waning arousal and impaired attention is observed in many SARS-CoV-2 positive patients, which is worsened due to isolation and excessive use of PPE (Sher *et al.* 2020). Nearly 66% of patients diagnosed with positive SARS-CoV-2 infection present some form of altered mental status including delirium (Hosseini *et al.* 2020). Given the complex nature of the manifestation, not much is known about the pathophysiology of delirium in COVID-19 infected patients. Delirium is not age restricted and equally affects the old and young population of SARS-CoV-2-positive patients (Palomar-Ciria *et al.* 2020; Beach *et al.* 2020).

The pathophysiology of the different cognitive and behavioural deficits in infected patients needs to be studied. Aberrant expression of the neurotransmitter nitric oxide (NO) may be associated with neuropathological conditions related to COVID-19. Angiotensin II which is upregulated in these patients reportedly decreases production of NO, and thus its concentration in the brain. This may result in the neuropathological conditions associated with COVID-19, although further experimental data is needed for confirmation (Annweiler *et al.* 2020).

Clinically hyperactive delirium is managed by administration of antipsychotics and sedatives (Kotfis *et al.* 2020), but their usage is still debatable as far as the first line medication of choice is concerned (Rogers *et al.* 2020). Current clinical practice is to initiate pharmacological intervention with low dosage of sedative lorazepam or haloperidol and subsequently escalate the dose if needed (Shrikant Kulkarni 2018; March *et al.* 2019). However, benzodiazepines are contradicted as a therapy for COVID-19-related delirium since it may cause respiratory depression (Gupta *et al.* 2020a).

8. Conclusions

There is now sufficient evidence available about how the Coronavirus affects the respiratory system leading to fever, cough, cold and breathing problems. However, coronaviruses also affect the CNS and PNS. The presence of virus in CNS and PNS is associated with early or delayed onset of neurological symptoms such as headache, dizziness, seizures, impaired consciousness, loss of smell, conjunctivitis and ocular abnormalities. Nevertheless, these neurological symptoms are not common in COVID-19 outbreaks. Patients presenting with neurological symptoms appear to be fewer in number compared with those presenting with respiratory distress. Identifying neurological problems such as stroke and encephalitis is crucial since they can cause lifetime disability and these patients may require long-term care. Assessment of CNS-related abnormalities should be included for patients who are COVID-19 positive for collecting evidence to piece together the mode of action of the virus in causing neurological distress. Further investigations on the mode of entry of this virus into specific regions of the brain and retina would also be useful to understand the CNS connections of SARS-CoV-2. These studies will help alleviate the global health burden due to the novel Coronavirus, as well as address the social and economic costs due to neurological complications in COVID-19 patients.

References

Aaroe A, Harrison R, Majd N, *et al.* 2020. A snapshot of the impact of Covid-19 on patients with nervous system tumors. *Neuro-Oncol.* **22** ii27

Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, *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

Amarenco P, Kim JS, Labreuche J, *et al.* 2019 Treat stroke to target trial design: first trial comparing two LDL targets in patients with atherothrombotic strokes. *Eur. Stroke J.* **4** 271–280

Annweiler C, Bourgeais A, Faucon E, Cao Z, Wu Y and Sabatier JM 2020 Neurological, cognitive, and behavioral disorders during COVID-19: The nitric oxide track. *J. Am. Geriatr. Soc.* **68** 1922–1923

Asadi-Pooya AA 2020 Seizures associated with coronavirus infections. *Seizure* **79** 49–52

Baig AM 2020 Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci. Therap.* **26** 499

Baig AM, Khaleeq A, Ali U and 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** 995–998

Balloy G, Leclair-Visonneau L, Péréon Y, Magot A, Peyre A, Mahé PJ and Derkinderen P 2020 Non-lesional status epilepticus in a patient with coronavirus disease 2019. *Clin. Neurophysiol.* **131** 2059–2061

Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, Fricchione GL and Smith FA 2020 Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. *Gen. Hosp. Psychiatr.* **65** 47–53

Belyhun Y, Moges F, Endris M, *et al*. 2018 Ocular bacterial infections and antibiotic resistance patterns in patients attending Gondar Teaching Hospital, Northwest Ethiopia. *BMC Res. Notes* **11** 1–7

Bernard-Valnet R, Pizzarotti B, Anichini A, *et al*. 2020 Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection. *Eur. J. Neurol.* **27** e43–e44

Bilbul M, Paparone P, Kim AM, Mutalik S and Ernst CL 2020 Psychopharmacology of COVID-19. *Psychosomatics* **61** 411–427

Borges do Nascimento IJ, Cacic N, Abdulazeem HM,, *et al*. 2020 Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J. Clin. Med.* **9** 941

Butowt R and Bilinska K 2020 SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. *ACS Chem. Neurosci.* **11** 1200–1203

Carod-Artal FJ 2020 Neurological complications from coronavirus and COVID-19. *Rev. Neurol.* **70** 311–322

Cascella M, Rajnik M, Aleem A, Dulebohn SC and Di Napoli R 2021 Features, Evaluation, and Treatment of Coronavirus (COVID-19); in *StatPearls* [Internet] (Treasure Island, FL: StatPearls Publishing)

Chong PF, Yoshida T, Yuasa S, Mori H, Tanaka-Taya K and Kira R 2020 Acute flaccid myelitis with neuroradiological finding of brachial plexus swelling. *Pediatr. Neurol.* **109** 85–88

Cipriano M, Ruberti E and Giacalone A 2020 Gastrointestinal infection could be new focus for Coronavirus diagnosis. *Cureus* **12** e7422

Cooper KW, Brann DH, Farruggia MC, *et al*. 2020 COVID-19 and the chemical senses: supporting players take center stage. *Neuron* **107** 219–233

Cunha-Vaz J, Bernardes R and Lobo C 2011 Blood-retinal barrier. *Eur. J. Ophthal.* **21** 3–9

De Felice FG, Tovar-Moll F, Moll J, Munoz DP and Ferreira ST 2020 Severe acute respiratory syndrome coronavirus **2** (SARS-CoV-2) and the central nervous system. *Trends Neurosci.* **43** 355–357

Donoso Mantke O, McCulloch E, Wallace PS, Yue C, Baylis SA and Niedrig M 2018 External quality assessment (EQA) for molecular diagnostics of Zika virus: experiences from an international EQA programme, 2016–2018. *Viruses* **10** 491

Dubé M, Le Coupanec A, Wong AH, Rini JM, Desforges M and Talbot PJ 2018 Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J. Virol.* **92** e00404–e00418

Eliezer M, Hautefort C, Hamel AL, Verillaud B, Herman P, Houdart E and Eloit C 2020 Sudden and complete olfactory loss of function as a possible symptom of COVID-19. *JAMA Otolaryngol. Head Neck Surg.* **146** 674–675

Ellul MA, Benjamin L, Singh B, *et al*. 2020 Neurological associations of COVID-19. *Lancet Neurol.* **19** 767–783

McArthur L, Sakthivel D, Ataide R, Chan F, Richards JS and Narh CA 2020 Review of burden, clinical definitions, and management of COVID-19 cases. *Am. J. Trop. Med. Hygiene* **103** 625–638

Filatov A, Sharma P, Hindi F and Espinosa PS 2020 Neurological complications of Coronavirus disease (COVID-19): Encephalopathy. *Cureus* **12** e7352

Ferner R, Murray P and Aronson J 2020 Spreading SARS-CoV-2 through ocular fluids *https://www.cebm.net/covid-19/spreading-sars-cov-2-through-ocular-fluids/*

Francis A and Parsh B 2020 Acute flaccid myelitis: an overview. *Nursing* **50** 15–17

Grippo A, Assenza G, Scarpino M, *et al*. 2020 Electroencephalography during SARS-CoV-2 outbreak: practical recommendations from the task force of the Italian Society of Neurophysiology (SINC), the Italian League Against Epilepsy (LICE), and the Italian Association of Neurophysiology Technologists (AITN). *Neurol. Sci.* **41** 2345–2351

Giacomelli A, Pezzati L, Conti F, *et al*. 2020 Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus **2** infection: a cross-sectional study. *Clin. Infect. Dis.* **71** 889–890

Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, Ahuja J, Sengupta D and Ahuja G 2021 The cellular basis of loss of smell in 2019-nCoV-infected individuals. *Brief. Bioinform.* **22** 873–881

Ha SH, Kim YJ, Heo SH, Chang DI and Kim BJ 2020 Prediction of deep vein thrombosis by ultrasonography and D-dimer in Asian patients with ischemic stroke. *BMC Neurol.* **20** 1–6

Haddad S, Tayyar R, Risch L, Churchill G, Fares E, Choe M and Montemuro P 2020 Encephalopathy and seizure activity in a COVID-19 well controlled HIV patient. *ID Cases* **21** e00814

Helms J, Kremer S, Merdji H, *et al*. 2020 Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med.* **382** 2268–2270

Hess DC and Fagan SC 2010 Repurposing an old drug to improve the use and safety of tissue plasminogen activator for acute ischemic stroke: minocycline. *Pharmacother. J. Human Pharmacol. Drug Ther.* **30** 55S-61S

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

Coelho DH, Reiter ER, Budd SG, Shin Y, Kons ZA and Costanzo RM 2021 Quality of life and safety impact of COVID-19 associated smell and taste disturbances. *Am. J. Otolaryngol.* **42** 103001

Hosseini AA, Shetty AK, Sprigg N, Auer DP and Constantinescu CS 2020 Delirium as a presenting feature in COVID-19: Neuroinvasive infection or autoimmune encephalopathy? *Brain Behav. Immun.* **88** 68–70

Huang YH, Jiang D and Huang JT 2020 SARS-CoV-2 Detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav. Immun.* **87** 149

Hummel T, Landis BN and Hüttenbrink KB 2011 Smell and taste disorders. *GMS Curr. Top. Otorhinolaryngol. Head Neck Surg.* **10** Doc04

Iroegbu JD, Ifenatuoha CW and Ijomone OM 2020 Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2. *Neurol. Sci.* **41** 1329–1337

Kandemirli SG, Dogan L, Sarikaya ZT, *et al*. 2020 Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology* **297** E232–E235

Kandemirli SG, Altundag A, Yildirim D, Sanli DE and Saatci O 2021 Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. *Acad. Radiol.* **28** 28–35

Kaye R, Chang CD, Kazahaya K, Brereton J and Denneny JC III 2020 COVID-19 anosmia reporting tool: initial findings. *Otolaryngol. Head Neck Surg.* **163** 132–134

Keaney J and Campbell M 2015 The dynamic blood–brain barrier. *FEBS J.* **282** 4067–4079

Komurasaki Y, Nagineni CN, Wang Y and Hooks JJ 1996 Virus RNA persists within the retina in coronavirus-induced retinopathy. *Virology* **222** 446–450

Kotfis K, Roberson SW, Wilson JE, *et al*. 2020 COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? *Anaesthesiol. Intensive Ther.* **52** 132

Kulkarni NS 2018 Lorazepam Added to haloperidol effective for agitated delirium in end-of-life cancer patients. *Am. Fam. Physician.* 97

Lechien JR, Chiesa-Estomba CM, De Siati DR, *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. Oto-Rhino-Laryngol.* **277** 2251–2261

Lee JC and Chong JW 2020 Ventilation-perfusion scans during the Coronavirus disease 2019 (COVID-19) outbreak. *J. Am. Coll. Radiol.* **17** 698

Li YC, Bai WZ and 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** 552–555

Manangeeswaran M, Kielczewski JL, Sen HN, *et al*. 2018 ZIKA virus infection causes persistent chorioretinal lesions. *Emerg. Microbes Infect.* **7** 1–5

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

March KL, Twilla JD, Reaves AB, Self TH, Slayton MM, Bergeron JB and Sakaan SA 2019 Lorazepam versus chlordiazepoxide for the treatment of alcohol withdrawal syndrome and prevention of delirium tremens in general medicine ward patients. *Alcohol* **81** 56–60

Matías-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J and Matias-Guiu JA 2020 Should we expect neurological symptoms in the SARS-CoV-2 epidemic? *Neurología* **35** 170–175

McLaren N, Lopez A, Kidd S, Zhang J, Nix WA, Link-Gelles R, Lee A and Routh JA 2020 Characteristics of patients with acute flaccid myelitis, united states, 2015–2018. *Emerg. Infect. Dis.* **26** 212

Menni C, Valdes A, Freydin MB, *et al.* 2020 Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *MedRxiv*

Montalvan V, Lee J, Bueso T, De Toledo J and Rivas K 2020 Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin. Neurol. Neurosurg.* **194** 105921

Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C and Vogrig A 2020 Stroke in patients with SARS-CoV-2 infection: case series. *J. Neurol.* **267** 2185–2192

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

Moshayedi P, Ryan TE, Mejia LL, Nour M and Liebeskind DS 2020 Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion associated with coronavirus infection. *Front. Neurol.* **11** 353

Murphy OC and Pardo CA 2020 Acute flaccid myelitis: a clinical review. *Sem. Neurol.* **40** 211–218

Netland J, Meyerholz DK, Moore S, Cassell M and Perlman S 2008 Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J. Virol.* **82** 7264–7275

Nie S, Han S, Ouyang H and Zhang Z 2020 Coronavirus Disease 2019-related dyspnea cases difficult to interpret using chest computed tomography. *Resp. Med.* **167** 105951

Palasca O, Santos A, Stolte C, Gorodkin J and Jensen LJ 2018 TISSUES 2.0: an integrative web resource on mammalian tissue expression. *Database (Oxford)* 2018 bay003

Palomar-Ciria N, Del Valle PB, Hernández-Las Heras MA and Martínez-Gallardo R 2020 Schizophrenia and COVID-19 delirium. *Psychiatry Res.* **290** 113137

Perlman S and McCray PB Jr 2013 Person-to-person spread of the MERS coronavirus–an evolving picture. *N. Engl. J. Med.* **369** 466–467

Politi LS, 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

Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S and Griffith B 2020 COVID-19–associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology* **296** E119–E120

Ramani A, Müller L, Ostermann PN, *et al*. 2020 SARS-CoV-2 targets neurons of 3D human brain organoids. *EMBO J.* **39** e106230

Reddy ST, Garg T, Shah C, *et al*. 2020 Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. *Case Rep. Neurol.* **12** 199–209

Reynolds JL and Mahajan SD 2021 SARS-COV2 Alters blood brain barrier integrity contributing to neuro-inflammation. *J. Neuroimm. Pharmacol.* **16** 4–6

Rhea EM, Logsdon AF, Hansen KM, *et al*. 2021 The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice. *Nat. Neurosci.* **24** 368–378

Van Riel D, Verdijk R and Kuiken T 2015 The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J. Pathol.* **235** 277–287

Rogers JP, 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

Sato T, Sato S, Yamagami H, *et al*. 2020 D-dimer level and outcome of minor ischemic stroke with large vessel occlusion. *J. Neurol. Sci.* **413** 116814

Savarin C and Bergmann CC 2018 Fine tuning the cytokine storm by IFN and IL-10 following neurotropic Coronavirus encephalomyelitis. *Front. Immunol.* **9** 3022

Sayin İ, Yaşar KK and Yazici ZM 2020 Taste and smell impairment in COVID-19: An AAO-HNS anosmia reporting tool-based comparative study. *Otolaryngol. Head Neck Surg.* **163** 473–479

Seah I and Agrawal R 2020 Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocular Immunol. Inflam.* **28** 391–395

Serrano-Castro PJ, Estivill-Torrús G, Cabezudo-García P, *et al*. 2020 Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? *Neurología* **35** 245–251

Sher Y, Rabkin B, Maldonado JR and Mohabir P 2020 COVID-19–associated hyperactive intensive care unit delirium with proposed pathophysiology and treatment: a case report. *Psychosomatics* **61** 544

Singh PK, Guest JM, Kanwar M, Boss J, Gao N, Juzych MS, Abrams GW, Yu FS and Kumar A 2017 Zika virus infects cells lining the blood-retinal barrier and causes chorioretinal atrophy in mouse eyes. *JCI Insight* **2** e92340

Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR and Liu ZS 2020a Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J. Pediatr.* **16** 251–259

Sun CB, Wang YY, Liu GH and Liu Z 2020b Role of the eye in transmitting human coronavirus: what we know and what we do not know. *Front. Public Health* **8** 155

Tejada Meza H, Lambea Gil Á, Sancho Saldaña A, *et al*. 2020 Ischaemic stroke in the time of coronavirus disease 2019. *Eur. J. Neurol.* **27** 1788–1792

Tong JY, Wong A, Zhu D, Fastenberg JH and Tham T 2020 The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol. Head Neck Surg.* **163** 3–11

Toniati P, Piva S, Cattalini M, *et al*. 2020 Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun. Rev.* **19** 102568

Tsivgoulis G, Palaiodimou L, Katsanos AH, *et al*. 2020 Neurological manifestations and implications of COVID-19 pandemic. *Ther. Adv. Neurol. Disord.* **13** 1756286420932036

Tuttolomondo A, Di Raimondo D, Pecoraro R, *et al*. 2016 Early high-dosage atorvastatin treatment improved serum immune-inflammatory markers and functional outcome in acute ischemic strokes classified as large artery atherosclerotic stroke: a randomized trial. *Medicine*

Vaira LA, Deiana G, Fois AG, *et al*. 2020 Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck* **42** 1252–1258

Vonck K, Garrez I, De Herdt V, Hemelsoet D, Laureys G, Raedt R and Boon P 2020 Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2. *Eur. J. Neurol.* **27** 1578–1587

Wan Y, Graham R, Baric R and Li F 2020 An analysis based on decade-long structural studies of SARS 3. *J. Virol.* **94** e00127-e220

Wang Y, Detrick B, Yu ZX, Zhang J, Chesky L and Hooks JJ 2000 The role of apoptosis within the retina of coronavirus-infected mice. *Invest. Ophthalmol. Visual Sci.* **41** 3011–3018

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS and McLellan JS 2020 Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* **367** 1260–1263

Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C and Yang C 2020 Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav. Immun.* **87** 18–22

Xu XW, Wu XX, Jiang XG, *et al*. 2020a Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* **368** m606

Xu N, Fu Y, Wang S, Li S and Cai D 2020b High level of D-dimer predicts ischemic stroke in patients with infective endocarditis. *J. Clin. Lab. Anal.* **34** e23206

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T and Chen Q 2020c High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int. J. Oral Sci.* **12** 1–5

Yaghi S, Ishida K, Torres J, *et al*. 2020 SARS-CoV-2 and stroke in a New York healthcare system. *Stroke* **51** 2002–2011

Yan CH, Faraji F, Prajapati DP, Boone CE and DeConde AS 2020 Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int. Forum Allergy Rhinol.* **10** 806–813

Zhang H, Kang Z, Gong H, *et al*. 2020 Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* **69** 1010–1018

Zhang L, Lv H, Zhang Q, Wang D, Kang X, Zhang G and Li X 2019 Association of SLCO1B1 and ABCB1 genetic variants with atorvastatin-induced myopathy in patients with acute ischemic stroke. *Curr. Pharmaceut. Design* **25** 1663–1670

Zhao J, Rudd A and Liu R 2020 Challenges and potential solutions of stroke care during the Coronavirus disease 2019 (COVID-19) outbreak. *Stroke* **51** 1356–1357

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