Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER TWO

Covid-19, nervous system pathology, and Parkinson's disease: Bench to bedside

Aron Emmi[a], Iro Boura[b], Vanessa Raeder[c,d,h], Donna Mathew[e], David Sulzer[f], James E. Goldman[g], and Valentina Leta[c,h,*]

[a]Institute of Human Anatomy, Department of Neuroscience, University of Padova, Padova, Italy
[b]Department of Neurology, University Hospital of Heraklion, Crete, Greece
[c]Parkinson's Foundation Centre of Excellence, King's College Hospital NHS Foundation Trust, London, United Kingdom
[d]Department of Neurology, Technical University Dresden, Dresden, Germany
[e]Neuroscience and Mental Health Research Institute, School of Medicine, Cardiff University, Cardiff, United Kingdom
[f]Departments of Psychiatry, Neurology, Pharmacology, Columbia University Medical Center, New York State Psychiatric Institute, New York, United States
[g]Department of Pathology and Cell Biology, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Vagelos College of Physicians and Surgeons, Columbia University and the New York Presbyterian Hospital, New York, NY, United States
[h]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
*Corresponding author: e-mail address: valentina.leta@kcl.ac.uk

Contents

Abstract

Coronavirus disease 2019 (Covid-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is primarily regarded as a respiratory disease; however, multisystemic involvement accompanied by a variety of clinical manifestations, including neurological symptoms, are commonly observed. There is, however, little evidence supporting SARS-CoV-2 infection of central nervous system cells, and

International Review of Neurobiology, Volume 165
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2022.06.006

neurological symptoms for the most part appear to be due to damage mediated by hypoxic/ischemic and/or inflammatory insults. In this chapter, we report evidence on candidate neuropathological mechanisms underlying neurological manifestations in Covid-19, suggesting that while there is mostly evidence against SARS-CoV-2 entry into brain parenchymal cells as a mechanism that may trigger Parkinson's disease and parkinsonism, that there are multiple means by which the virus may cause neurological symptoms.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel, highly contagious, and pathogenic strain of the Coronaviruses (CoV) family, which has caused the pandemic of coronavirus disease 2019 (Covid-19) (Hu, Guo, Zhou, & Shi, 2021; Lai, Shih, Ko, Tang, & Hsueh, 2020). Emerging in late 2019, SARS-CoV-2 has taken a toll on global morbidity and mortality as a major public health issue. Although manifesting primarily as a respiratory disease, there are numerous reports of neurological manifestations of Covid-19, either presenting as new symptoms or disorders (e.g., stroke, Guillain-Barré syndrome) or as the exacerbation of pre-existing symptoms of known chronic neurological conditions (Antonini, Leta, Teo, & Chaudhuri, 2020; Kubota & Kuroda, 2021; Leta et al., 2021; Ousseiran, Fares, & Chamoun, 2021). These observations, along with the detection of the virus in post-mortem tissue and cerebrospinal fluid (CSF) (Lewis et al., 2021; Mukerji & Solomon, 2021; Tandon et al., 2021) raise the question of whether SARS-CoV-2 enters the human brain or causes neurological symptoms because of the systemic illness, notably hypoxia and inflammation.

2. SARS-CoV-2 receptors

SARS-CoV-2 shares 80% of its genome with SARS-CoV and 50% with MERS-CoV, with homologies extending to the protein spike (S), which after cleavage by the transmembrane protease serine 2 (TMPRSS2), can bind host membrane proteins acting as viral receptors (Hoffmann et al., 2020; Xu et al., 2020).

The main viral receptor for SARS-CoV-2 and other CoV is angiotensin-converting enzyme 2 (ACE2), an enzyme that catalyzes the cleavage of angiotensin I into angiotensin 1–9 and angiotensin II into the vasodilator angiotensin 1–7 (Wang et al., 2020). ACE2 is a transmembrane protein that

is widely expressed in human tissues, and while its expression in brain neurons and astrocytes has not been clearly demonstrated, it is expressed in brain vessels (Hamming et al., 2004) and hypoxic insult appears to upregulate its expression (Zhang et al., 2009).

Similarly to MERS-CoV, virus cellular endocytosis may be alternatively mediated by sialic acid residues, which are located on plasma membrane proteins of several type of cells, including neurons (Fantini, Di Scala, Chahinian, & Yahi, 2020) or by the lectin CD209L, which is a receptor for SARS-CoV (Jeffers et al., 2004), although such alternative receptors have not been clearly demonstrated for SARS-CoV-2.

3. Neuroinflammation in post-mortem Covid-19 brain

Neuroinflammation is prominent in Covid-19 and characterized by lympho-monocytic infiltrations, microglial activation and microglial nodules. Lympho-monocytic perivascular cuffing and infiltration have been reported by most authors, with a predominance of perivascular CD68+ monocytes/macrophages and CD8+ T-cells (Lee et al., 2021; Matschke et al., 2020; Meinhardt et al., 2021; Schwabenland et al., 2021; Thakur et al., 2021), although lymphocyte accumulation appears mild compared to that in viral encephalitis, such as from Herpes viruses.

In all studies examining microglial cells, authors identified prominent microglial activation with upregulation of MHC-II proteins (HLA-DR) and increased lysosomal activity (CD68+), while maintaining a homeostatic microglial marker TMEM119 (Deigendesch et al., 2020; Matschke et al., 2020; Meinhardt et al., 2021; Schwabenland et al., 2021; Thakur et al., 2021). Similarly, evidence of neuronophagia was documented by most authors with prominent involvement of the lower brainstem at the level of the medullary tegmentum, the midline raphe, inferior olivary nucleus, and the dorsal pons (Al-Dalahmah et al., 2020; Deigendesch et al., 2020; Matschke et al., 2020; Meinhardt et al., 2021; Schwabenland et al., 2021; Thakur et al., 2021). Microglial nodules with associated CD8+/CD3+ T-cell clusters were also documented in most, but not all, Covid-19 patients, in contrast to non-Covid-19 controls and ExtraCorporeal Membrane Oxygenation (ECMO) patients, who displayed no instances of microglial nodules and neuronophagia (Schwabenland et al., 2021), although we have observed activated microglia and nodules in the brainstems of patients with severe respiratory distress (JE Goldman, P Canoll, unpublished observations). Deep spatial profiling of the local immune response in Covid-19

brains by imaging mass spectrometry revealed significant immune activation in the medulla and olfactory bulb with a prominent role mediated by CD8+ T-cell—microglia crosstalk in the parenchyma (Schwabenland et al., 2021). Conversely, Deigendesch and colleagues found significant differences in HLA-DR+ activated microglia when comparing Covid-19 subjects to non-septic controls, but no differences were found with patients who had died under septic conditions; according to the authors, this may represent a histopathological correlate of critical illness-related encephalopathy and hypoxia, rather than a Covid-19-specific finding (Deigendesch et al., 2020).

Neurological symptoms of Covid-19 occur regularly without detection of SARS-CoV-2 in CSF samples, but there is evidence for autoantibody formation. In a cohort of 102 Covid-19 patients, where almost 60% presented some form of neurological symptoms, CSF anti-neuronal autoantibodies were detected in 35% of those tested (Fleischer et al., 2021). In a study of critically ill Covid-19 patients ($n = 11$) with unexplained neurological sequelae, anti-neuronal autoantibodies were found in the CSF of all patients, as well as in their serum, suggesting that multiple autoantigens and a potential molecular mimicry to SARS-CoV-2 might mediate these symptoms, especially those related to hyperexcitability (myoclonus, seizures) (Franke et al., 2021). The above findings might guide clinicians to consider administering immunotherapy in selected patients.

Thus, while most studies are consistent on the overall neuroinflammatory conditions occurring in the context of Covid-19, with particular focus on microgliosis and microglia—T-cell crosstalk, disagreements on the source of inflammation are unresolved. In particular, it is not clear how much might be due to an ongoing systemic inflammation/cytokine storm, and whether and how frequent comorbidities, such as hypertension, diabetes, cardiovascular disease or neurodegenerative conditions, and hypoxic/ischemic damage may influence microgliosis and brain inflammation.

4. Little evidence of neuro-invasion in post-mortem Covid-19 cases

Neurotropism has been established for many species of the CoV family, including Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV-1) (Zubair et al., 2020), while there have been reports for persistent chronic infections of particular CoV strains in human neuronal cell lines or in the brain of patients with

neurodegenerative disorders (Arbour et al., 1999; Murray, Brown, Brian, & Cabirac, 1992). SARS-CoV-2 has been speculated to possess a neuroinvasive potential (Koyuncu, Hogue, & Enquist, 2013; Verstrepen, Baisier, & De Cauwer, 2020; Yachou, El Idrissi, Belapasov, & Ait Benali, 2020), and has been claimed in experimental models (Bullen et al., 2020). However, while there is significant evidence for neuroinflammation in the brain induced by SARS-CoV-2, as detailed here, neuropathological findings at this juncture do not support significant infection of brain cells.

To date, the presence of viral peptides in brain, determined by immunostaining, has been reported only in a small set of patients and in a few cells, and has not been constantly reproduced throughout available studies (Lee et al., 2021; Matschke et al., 2020; Meinhardt et al., 2021; Schwabenland et al., 2021; Solomon et al., 2020; Thakur et al., 2021; Yang et al., 2021). While most studies agree on the detection of low or undetectable viral RNA levels using RT-PCR analyses, detection of viral RNA in blood and blood vessels of the investigated samples cannot be excluded. In contrast, immunoperoxidase and immunofluorescent staining, imaging mass spectrometry and in situ hybridization that provide for the spatial localization of viral proteins/RNA have failed to consistently detect viral antigens or RNA. Matschke and colleagues found sparse immunoreactive cells throughout the brainstem, without specific topographic localization, but also detected distinct immunoreactivity of the glossopharyngeal and vagus nerve bundles (CN IX-X) in a subset of patients, and suggested SARS-CoV-2 retrograde spread through these cranial nerves toward the medulla (Matschke et al., 2020). This is also supported by the detection of SARS-CoV-2 antigen and genomic sequences in the carotid body of Covid-19 subjects (Porzionato et al., 2021). However, there was no apparent association between the presence of viral antigens and neuropathological changes.

Several studies have detected viral proteins and RNA in the olfactory mucosa through immunohistochemistry, immunofluorescence and in-situ hybridization, as well as electron microscopy (Khan et al., 2021; Meinhardt et al., 2021; Zazhytska et al., 2022). Meinhardt et al. observed SARS-CoV-2 spike protein in primary olfactory neurons of the olfactory mucosa, suggesting an olfactory-transmucosal spread of the virus. This was supported by the detection of viral RNA at the level of the olfactory bulb and medulla, even though viral proteins were not detected in non-vascular cells. Furthermore, SARS-CoV-2 immunoreactive endothelial cells associated with microvascular injury and micro-thromboses were

found in a subset of Covid-19 patients at the level of the medulla. Conversely, two recent studies found virus in sustentacular cells of the olfactory epithelium, but not in olfactory neurons (Khan et al., 2021; Zazhytska et al., 2022). The latter detected reorganization of nuclear architecture and downregulation of olfactory receptors, as well as their signaling pathways, in the olfactory neurons, suggesting a non-cell autonomous cause of anosmia (Zazhytska et al., 2022).

Schwabenland and colleagues detected viral antigen in ACE2-positive cells enriched in the vascular compartment (Schwabenland et al., 2021). According to the authors, this finding was linked to vascular proximity and ACE2 expression, and was correlated to the perivascular immune activation patterns of CD8+ and CD4+ T-cells and myeloid- and microglial-cell subsets, indicating a fundamental role of the vascular and perivascular compartment, as well as a blood–brain barrier impairment in mediating Covid-19-specific neuroinflammation.

Two studies of single nucleus RNA sequencing of brains of COVID-19 patients detected broad perturbations, with upregulation of genes involved in innate antiviral response and inflammation, microglia activation and neurodegeneration, but found no direct evidence of viral RNA (Fullard et al., 2021; Yang et al., 2021). Other authors have not detected viral proteins/RNA through immunohistochemistry or in situ hybridization, even though viral genomic sequences were found with RT-PCR assays (Lee et al., 2021; Solomon et al., 2020; Thakur et al., 2021).

Hence, SARS-CoV-2 invasion of the CNS remains to be definitively shown, and much evidence points against the presence of detectable virus, although there are reports of rare instances of the presence of viral antigens in brain cells.

5. SARS-CoV-2 and parkinsonism

Understandably, the idea that neuronal infection by SARS-CoV-2 might predispose to parkinsonism has been a source of great concern (Beauchamp, Finkelstein, Bush, Evans, & Barnham, 2020; Bouali-Benazzouz & Benazzouz, 2021; Brundin, Nath, & Beckham, 2020), although, fortunately, there is little evidence supporting this response. Although there are no reports of CoV-associated parkinsonism, antibodies against common CoV have been detected in the CSF of people with Parkinson's Disease (PwP, PD) in significantly higher titers compared to controls, while there was evidence of post-encephalitic parkinsonism in

mice infected with a CoV strain (MHV-A59) (Fazzini, Fleming, & Fahn, 1992; Fishman et al., 1985). In a recent literature review, 20 cases of new-onset parkinsonism developing during or shortly after a SARS-CoV-2 infection have been described, presenting a variety of different subjacent mechanisms (Boura & Chaudhuri, 2022). Although these cases do not suffice to support an etiological association between the two entities, the concept of vigilance in the long-term is highlighted.

The concerns on Covid-19 influence on Parkinson's disease stem both from the 1917 Spanish flu/von Economo's encephalitis pandemics as well an association of numerous viruses with the development of transient or permanent parkinsonism (Jang, Boltz, Webster, & Smeyne, 2009), including reports that anti-viral treatment and vaccination are associated with a decreased risk of parkinsonism in humans and animal models (Lin et al., 2019; Sadasivan, Sharp, Schultz-Cherry, & Smeyne, 2017). It has been suggested that pathogens contribute to PD pathogenesis, particularly after the age of 50 in individuals with or without a susceptible genetic substrate (Beauchamp et al., 2020; Tanner et al., 1999). Braak and others have suggested that neurotropic pathogens may infect the CNS via the nasal or gastric pathway, both of which are sites of early pathology in PD (Hawkes, Del Tredici, & Braak, 2007; Klingelhoefer & Reichmann, 2015) and viral-related inflammation might render the CNS susceptible to preceding or subsequent stressors (Sulzer, 2007). Indeed, a meta-analysis demonstrated that a past history of an infection was associated with a 20% higher risk of presenting PD in the future, although this was significant only for bacterial and not viral infections (Meng, Shen, & Ji, 2019). An association between past CNS infections, particularly if multiple hospitalizations preceded, and a subsequent development of PD was described (Fang et al., 2012). Finally, epidemiological data from a large cohort of PD patients and controls indicates an increased PD frequency among occupations with a high risk for respiratory infections, such as teachers and health-care workers, (the "clustering of PD" theory) (Tsui, Calne, Wang, Schulzer, & Marion, 1999).

While there is little evidence at this time for a role for Covid-19 in increasing PD, there could be effects particularly on peripheral catecholamine systems. L-Dopa decarboxylase (DDC), an essential enzyme in the biosynthesis of dopamine and serotonin, is the most significantly coexpressed and coregulated gene with ACE2 in non-neuronal cell types, significantly affecting dopamine blood levels (Nataf, 2020). SARS-CoV-2 infection of monkey cell lines was found to induce downregulation of

DDC, an effect also noted with dengue and hepatitis C infections (Mpekoulis et al., 2021), pathogens associated with parkinsonism (Bopeththa & Ralapanawa, 2017; Tsai et al., 2016). DDC levels rose in nasopharyngeal tissues of asymptomatic or mild severity Covid-19 patients, while an inverse relationship was noted between SARS-CoV-2 RNA levels and DDC expression (Mpekoulis et al., 2021). Moreover, a dopamine D1 receptor agonist was found to suppress endotoxin-induced pulmonary inflammation in mice, suggesting that a potential protective role of dopamine in inflammation needs to be further explored (Bone, Liu, Pittet, & Zmijewski, 2017).

Vascular damage constitutes a recognized complication of Covid-19 (Siddiqi, Libby, & Ridker, 2021). A case of bilateral basal ganglia insult in the context of a thromboembolic encephalopathy without parkinsonism in a Covid-19 patient has been described (Haddadi, Ghasemian, & Shafizad, 2020).

6. Peripheral pathways that may contribute to neuroinflammation

6.1 Olfactory pathway

SARS-CoV-1 enters the brain of transgenic mice via the olfactory bulb, causing neuronal death without signs of encephalitis (Netland, Meyerholz, Moore, Cassell, & Perlman, 2008), while intranasal inoculation of MERS-CoV in transgenic mice led to high levels of the virus in the CNS, particularly in the thalamus and the brainstem (Li et al., 2016).

The characteristic clinical symptoms of hyposmia or anosmia in Covid-19, as well as hypogeusia or ageusia, which are quite prominent among affected patients (Guerrero et al., 2021) support the hypothesis of an involvement of the olfactory system (Lechien et al., 2020). An increased SARS-CoV-2 viral load in the nasal epithelium has been found by RT-PCR in situ hybridization and immunohistochemical staining methods (Meinhardt et al., 2021). Moreover, a prospective autopsy study in the Netherlands involving 21 patients who had succumbed to Covid-19 complications revealed extensive inflammation in the brain among other tissues, particularly focused in the olfactory bulbs and the medulla oblongata, although this study did not reveal presence of the virus in the brain (Schurink et al., 2020). Politi and colleagues described a case report of a Covid-19-positive woman with anosmia, who presented with subtle

hyperintensities in the olfactory bulbs and the right gyrus rectus in brain magnetic resonance imaging (MRI), although the authors highlighted that this was not a consistent finding among Covid-19 patients with smell dysfunction (Politi, Salsano, & Grimaldi, 2020). A recently published paper, exploring the findings of brain scans before and after a SARS-CoV-2 infection in a large sample of UK Biobank participants, showed significant reductions in gray matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus, along with prominent alterations in brain areas functionally connected to the primary olfactory cortex, suggestive of tissue damage (Douaud et al., 2022), although it is difficult to correlate the scan findings with cellular pathology. Furthermore, post-mortem brain MRI studies in 19 decedents of Covid-19 demonstrated an asymmetry in the olfactory bulbs in about 20% of the patients (Coolen et al., 2020). Post-mortem studies of Covid-19 patients detected the virus in the sustentacular cells of the olfactory epithelium, but not in the olfactory receptor neurons or the olfactory bulbs (Khan et al., 2021), as noted above.

6.2 Enteric pathways

With both respiratory and gastrointestinal symptoms being quite common in the context of Covid-19 (Cares-Marambio et al., 2021; Groff et al., 2021) and ACE2 being highly expressed in the alveolar epithelial type II cells and the intestinal endothelial cells (Williams et al., 2021), some researchers have suggested the potential of SARS-CoV-2 entry through the intestine (Lehmann et al., 2021; Mönkemüller, Fry, & Rickes, 2020; Zhang et al., 2020). RNA of the SARS-CoV-2 has been identified in stool samples and rectal swabs, even in cases with negative nasopharyngeal swabs (Tang, Schmitz, Persing, & Stratton, 2020). An autopsy study ($n = 21$) revealed SARS-CoV-2-infected cells in the respiratory and gastrointestinal tract, among other tissues, along with extensive inflammation in the medulla oblongata, implying a potential effect on the respiratory control center (Schurink et al., 2020). Many studies report inflammation in the medulla (see above), but the link between peripheral organs and the brain is not clear. One possible way in which systemic inflammation can influence medullary nuclei is the activation of vagal medullary afferents by inflammatory molecules. Thus, vagal endings contain receptors to IL-1β and are activated by this cytokine, subsequently activating neurons of the solitary nucleus, which then activate sympathetic output from the vagal nucleus and the nucleus ambiguous through the vagus nerve (Pavlov & Tracey, 2012).

6.3 Vascular pathways

Non-neuronal pathways of SARS-CoV-2 that might lead to neuroinflammation must be considered, including the hematogenous route. SARS-CoV-2 can enter the blood stream and either access and damage the endothelium of brain vasculature to cross the BBB, or trigger an inflammatory response, leading to breakdown of the BBB (Meinhardt et al., 2021; Wan et al., 2021).

Cerebrovascular disease, including ischemic and hemorrhagic strokes, constitutes a severe and common complication in Covid-19 (Tsivgoulis et al., 2020). The brains of patients who did not survive Covid-19 show acute cerebrovascular disease, including thrombotic microangiopathy and endothelial injury, without any evidence of vasculitis (Hernández-Fernández et al., 2020; Wan et al., 2021). Accumulating data suggests that Covid-19 is connected to a hypercoagulable state, which is closely related to inflammation and predisposes to macro- and microvascular thrombosis, resulting in arterial and venous infarcts (Abou-Ismail, Diamond, Kapoor, Arafah, & Nayak, 2020).

ACE2 is expressed in cells of the vasculature in the human brain, although the specific cell types have not been defined (Hamming et al., 2004). TMPRSS2 and NRP1 are also present in the endothelial cells of the vasculature (Wan et al., 2021). SARS-CoV-2 endothelitis has also been confirmed in autopsy studies concerning other human tissues (lungs, kidney, heart, liver, small intestine) (Varga et al., 2020). Moreover, Pellegrini and colleagues showed a leakage across the BBB, using a model of the human choroid plexus epithelial cells infected by SARS-CoV-2 (Pellegrini et al., 2020), although one has to consider the results of such in vitro studies carefully, since they may not reflect what occurs in the living brain.

On the other hand, a SARS-CoV-2 infection can cause an excessive systemic inflammatory response after triggering a cytokine storm in the periphery, resulting in a BBB disruption (Sulzer et al., 2020). Researchers have suggested that SARS-CoV-2 may infect immune cells, using them as a "trojan horse" to invade the CNS via the impaired BBB or activate different populations of immune cells, which may infiltrate the CNS, causing a secondary cytokine storm and thus neurologic manifestations (Pezzini & Padovani, 2020; Wan et al., 2021; Williams et al., 2021).

6.4 Hypoxia and ischemia

Finally, hypoxic/ischemic changes of the brain due to respiratory abnormalities and hypoperfusion in the context of Covid-19 appear likely to play a

crucial role in the development of secondary neurological manifestations (Sullivan & Fischer, 2021). Cases of hypoxic brain injury following Acute Respiratory Distress Syndrome (ARDS) have been described in the literature, including cases of parkinsonism, with the authors highlighting the possibility of silent hypoxia (Ayele et al., 2021; Fearon, Mikulis, & Lang, 2021; Radnis et al., 2020). However, the fact that neurological complications have been reported in the absence of any respiratory symptoms, suggest that alternative mechanisms mediate the virus-induced CNS insults (Ellul et al., 2020).

Hypoxic/ischemic pathology is particularly common in Covid-19, being reported in most studies (Matschke et al., 2020; Solomon et al., 2020; Thakur et al., 2021). Alterations were mostly widespread, and both acute and subacute findings could be appreciated at the level of the cortex, the basal ganglia, the hippocampus and, most notably, the brainstem. Hypoxic/ischemic damage can be associated with vascular pathology, with numerous reported cases presenting both ischemic and hemorrhagic infarcts (Lee et al., 2021; Matschke et al., 2020; Remmelink et al., 2020; Thakur et al., 2021). Reactive astrogliosis in the context of hypoxic/ischemic injuries was also commonly encountered, prominently involving the basal ganglia and the brainstem (Matschke et al., 2020; Meinhardt et al., 2021; Thakur et al., 2021). Microvascular pathology, fibrinogen leakage and small vessel thromboses were associated with ischemic and vascular pathology, representing a characteristic finding of the Covid-19 cohorts (Lee et al., 2021; Matschke et al., 2020; Meinhardt et al., 2021; Porzionato et al., 2021; Porzionato, Emmi, et al., 2021; Schwabenland et al., 2021). Small vessel platelet-enriched microthrombi were predominantly found in the basal ganglia, brainstem and cerebellum, often associated to microvascular injury and fibrinogen leakage. Several instances of SARS-CoV-2 immunoreactive endothelial cells in the context of vascular injury were also detected (Meinhardt et al., 2021), indicating a prominent role of SARS-CoV-2 infection in determining Covid-19 associated small vessel pathology.

7. Conclusion

Although Covid-19 caused by SARS-CoV-2 infection is mainly regarded as a respiratory disease, a variety of clinical manifestations, including neurological symptoms, often occur. The evidence available to date suggests that Covid-19 does not significantly contribute to the incidence of Parkinson's disease and that neurological clinical manifestations observed

in the context of Covid-19 are mainly secondary to an indirect damage by SARS-CoV-2 in peripheral systems, in contrast to infection of CNS neurons and astrocytes.

References

Abou-Ismail, M. Y., Diamond, A., Kapoor, S., Arafah, Y., & Nayak, L. (2020). The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thrombosis Research*, *194*, 101–115. https://doi.org/10.1016/j.thromres.2020.06.029.

Al-Dalahmah, O., Thakur, K. T., Nordvig, A. S., Prust, M. L., Roth, W., Lignelli, A., et al. (2020). Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage. *Acta Neuropathologica Communications*, *8*(1), 147. https://doi.org/10.1186/s40478-020-01024-2.

Antonini, A., Leta, V., Teo, J., & Chaudhuri, K. R. (2020). Outcome of Parkinson's disease patients affected by COVID-19. *Movement Disorders*, *35*(6), 905–908. https://doi.org/10.1002/mds.28104.

Arbour, N., Côté, G., Lachance, C., Tardieu, M., Cashman, N. R., & Talbot, P. J. (1999). Acute and persistent infection of human neural cell lines by human coronavirus OC43. *Journal of Virology*, *73*(4), 3338–3350. https://doi.org/10.1128/jvi.73.4.3338-3350.1999.

Ayele, B. A., Demissie, H., Awraris, M., Amogne, W., Shalash, A., Ali, K., et al. (2021). SARS-COV-2 induced parkinsonism: The first case from the sub-Saharan Africa. *Clinical Parkinsonism & Related Disorders*, *5*, 100116. https://doi.org/10.1016/j.prdoa.2021.100116.

Beauchamp, L. C., Finkelstein, D. I., Bush, A. I., Evans, A. H., & Barnham, K. J. (2020). Parkinsonism as a third wave of the COVID-19 pandemic? *Journal of Parkinson's Disease*, *10*(4), 1343–1353. https://doi.org/10.3233/JPD-202211.

Bone, N. B., Liu, Z., Pittet, J.-F., & Zmijewski, J. W. (2017). Frontline science: D1 dopaminergic receptor signaling activates the AMPK-bioenergetic pathway in macrophages and alveolar epithelial cells and reduces endotoxin-induced ALI. *Journal of Leukocyte Biology*, *101*(2), 357–365. https://doi.org/10.1189/jlb.3HI0216-068RR.

Bopeththa, B., & Ralapanawa, U. (2017). Post encephalitic parkinsonism following dengue viral infection. *BMC Research Notes*, *10*(1), 655. https://doi.org/10.1186/s13104-017-2954-5.

Bouali-Benazzouz, R., & Benazzouz, A. (2021). Covid-19 infection and parkinsonism: Is there a link? *Movement Disorders*, *36*(8), 1737–1743. https://doi.org/10.1002/mds.28680.

Boura, I., & Chaudhuri, K. R. (2022). Coronavirus disease 2019 and related parkinsonism: The clinical evidence thus far. *Movement Disorders Clinical Practice*. https://doi.org/10.1002/mdc3.13461.

Brundin, P., Nath, A., & Beckham, J. D. (2020). Is COVID-19 a perfect storm for Parkinson's disease? *Trends in Neurosciences*, *43*(12), 931–933. https://doi.org/10.1016/j.tins.2020.10.009.

Bullen, C. K., Hogberg, H. T., Bahadirli-Talbott, A., Bishai, W. R., Hartung, T., Keuthan, C., et al. (2020). Infectability of human BrainSphere neurons suggests neurotropism of SARS-CoV-2. *ALTEX*, *37*(4), 665–671. https://doi.org/10.14573/altex.2006111.

Cares-Marambio, K., Montenegro-Jiménez, Y., Torres-Castro, R., Vera-Uribe, R., Torralba, Y., Alsina-Restoy, X., et al. (2021). Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chronic Respiratory Disease*, *18*. https://doi.org/10.1177/14799731211002240.

Coolen, T., Lolli, V., Sadeghi, N., Rovai, A., Trotta, N., Taccone, F. S., et al. (2020). Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology*, *95*(14), e2016–e2027. https://doi.org/10.1212/wnl.0000000000010116.

Deigendesch, N., Sironi, L., Kutza, M., Wischnewski, S., Fuchs, V., Hench, J., et al. (2020). Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. *Acta Neuropathologica*, *140*(4), 583–586. https://doi.org/10.1007/s00401-020-02213-y.

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., et al. (2022). SARS-CoV-2 is associated with changes in brain structure in UK biobank. *Nature*. https://doi.org/10.1038/s41586-022-04569-5.

Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., et al. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, *19*(9), 767–783. https://doi.org/10.1016/S1474-4422(20)30221-0.

Fang, F., Wirdefeldt, K., Jacks, A., Kamel, F., Ye, W., & Chen, H. (2012). CNS infections, sepsis and risk of Parkinson's disease. *International Journal of Epidemiology*, *41*(4), 1042–1049. https://doi.org/10.1093/ije/dys052.

Fantini, J., Di Scala, C., Chahinian, H., & Yahi, N. (2020). Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *International Journal of Antimicrobial Agents*, *55*(5), 105960. https://doi.org/10.1016/j.ijantimicag.2020.105960.

Fazzini, E., Fleming, J., & Fahn, S. (1992). Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Movement Disorders*, 7(2), 153–158. https://doi.org/10.1002/mds.870070210.

Fearon, C., Mikulis, D. J., & Lang, A. E. (2021). Parkinsonism as a sequela of SARS-CoV-2 infection: Pure hypoxic injury or additional COVID-19-related response? *Movement Disorders*, *36*(7), 1483–1484. https://doi.org/10.1002/mds.28656.

Fishman, P. S., Gass, J. S., Swoveland, P. T., Lavi, E., Highkin, M. K., & Weiss, S. R. (1985). Infection of the basal ganglia by a murine coronavirus. *Science*, *229*(4716), 877–879. https://doi.org/10.1126/science.2992088.

Fleischer, M., Köhrmann, M., Dolff, S., Szepanowski, F., Schmidt, K., Herbstreit, F., et al. (2021). Observational cohort study of neurological involvement among patients with SARS-CoV-2 infection. *Therapeutic Advances in Neurological Disorders*, *14*. https://doi.org/10.1177/1756286421993701. 1756286421993701.

Franke, C., Ferse, C., Kreye, J., Reincke, S. M., Sanchez-Sendin, E., Rocco, A., et al. (2021). High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain, Behavior, and Immunity*, *93*, 415–419. https://doi.org/10.1016/j.bbi.2020.12.022.

Fullard, J. F., Lee, H. C., Voloudakis, G., Suo, S., Javidfar, B., Shao, Z., et al. (2021). Single-nucleus transcriptome analysis of human brain immune response in patients with severe COVID-19. *Genome Medicine*, *13*(1), 118. https://doi.org/10.1186/s13073-021-00933-8.

Groff, A., Kavanaugh, M., Ramgobin, D., McClafferty, B., Aggarwal, C. S., Golamari, R., et al. (2021). Gastrointestinal manifestations of COVID-19: A review of what we know. *The Ochsner Journal*, *21*(2), 177–180. https://doi.org/10.31486/toj.20.0086.

Guerrero, J. I., Barragán, L. A., Martínez, J. D., Montoya, J. P., Peña, A., Sobrino, F. E., et al. (2021). Central and peripheral nervous system involvement by COVID-19: A systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. *BMC Infectious Diseases*, *21*(1), 515. https://doi.org/10.1186/s12879-021-06185-6.

Haddadi, K., Ghasemian, R., & Shafizad, M. (2020). Basal ganglia involvement and altered mental status: A unique neurological manifestation of coronavirus disease 2019. *Cureus*, *12*(4), e7869. https://doi.org/10.7759/cureus.7869.

Hamming, I., Timens, W., Bulthuis, M. L., Lely, A. T., Navis, G., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*, *203*(2), 631–637. https://doi.org/10.1002/path.1570.

Hawkes, C. H., Del Tredici, K., & Braak, H. (2007). Parkinson's disease: A dual-hit hypothesis. *Neuropathology and Applied Neurobiology*, *33*(6), 599–614. https://doi.org/10.1111/j.1365-2990.2007.00874.x.

Hernández-Fernández, F., Sandoval Valencia, H., Barbella-Aponte, R. A., Collado-Jiménez, R., Ayo-Martín, Ó., Barrena, C., et al. (2020). Cerebrovascular disease in patients with COVID-19: Neuroimaging, histological and clinical description. *Brain*, *143*(10), 3089–3103. https://doi.org/10.1093/brain/awaa239.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, 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*(2), 271–280. https://doi.org/10.1016/j.cell.2020.02.052.

Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews. Microbiology*, *19*(3), 141–154. https://doi.org/10.1038/s41579-020-00459-7.

Jang, H., Boltz, D. A., Webster, R. G., & Smeyne, R. J. (2009). Viral parkinsonism. *Biochimica et Biophysica Acta*, *1792*(7), 714–721. https://doi.org/10.1016/j.bbadis.2008.08.001.

Jeffers, S. A., Tusell, S. M., Gillim-Ross, L., Hemmila, E. M., Achenbach, J. E., Babcock, G. J., et al. (2004). CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(44), 15748–15753. https://doi.org/10.1073/pnas.0403812101.

Khan, M., Yoo, S. J., Clijsters, M., Backaert, W., Vanstapel, A., Speleman, K., et al. (2021). Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*, *184*(24), 5932–5949. https://doi.org/10.1016/j.cell.2021.10.027.

Klingelhoefer, L., & Reichmann, H. (2015). Pathogenesis of Parkinson disease--the gut-brain axis and environmental factors. *Nature Reviews. Neurology*, *11*(11), 625–636. https://doi.org/10.1038/nrneurol.2015.197.

Koyuncu, O. O., Hogue, I. B., & Enquist, L. W. (2013). Virus infections in the nervous system. *Cell Host & Microbe*, *13*(4), 379–393. https://doi.org/10.1016/j.chom.2013.03.010.

Kubota, T., & Kuroda, N. (2021). Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: A systematic review. *Clinical Neurology and Neurosurgery*, *200*, 106349. https://doi.org/10.1016/j.clineuro.2020.106349.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, *55*(3), 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924.

Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., Horoi, M., Le Bon, S. D., Rodriguez, A., 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. *European Archives of Oto-Rhino-Laryngology*, *277*(8), 2251–2261. https://doi.org/10.1007/s00405-020-05965-1.

Lee, M. H., Perl, D. P., Nair, G., Li, W., Maric, D., Murray, H., et al. (2021). Microvascular injury in the brains of patients with Covid-19. *The New England Journal of Medicine*, *384*(5), 481–483. https://doi.org/10.1056/NEJMc2033369.

Lehmann, M., Allers, K., Heldt, C., Meinhardt, J., Schmidt, F., Rodriguez-Sillke, Y., et al. (2021). Human small intestinal infection by SARS-CoV-2 is characterized by a mucosal infiltration with activated CD8(+) T cells. *Mucosal Immunology*, *14*(6), 1381–1392. https://doi.org/10.1038/s41385-021-00437-z.

Leta, V., Rodríguez-Violante, M., Abundes, A., Rukavina, K., Teo, J. T., Falup-Pecurariu, C., et al. (2021). Parkinson's disease and post–COVID-19 syndrome: The Parkinson's long-COVID Spectrum. *Movement Disorders*, *36*(6), 1287.

Lewis, A., Frontera, J., Placantonakis, D. G., Lighter, J., Galetta, S., Balcer, L., et al. (2021). Cerebrospinal fluid in COVID-19: A systematic review of the literature. *Journal of the Neurological Sciences*, *421*, 117316. https://doi.org/10.1016/j.jns.2021.117316.

Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A. K., Reznikov, L. R., et al. (2016). Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *The Journal of Infectious Diseases*, *213*(5), 712–722. https://doi.org/10.1093/infdis/jiv499.

Lin, W. Y., Lin, M. S., Weng, Y. H., Yeh, T. H., Lin, Y. S., Fong, P. Y., et al. (2019). Association of Antiviral Therapy with Risk of Parkinson disease in patients with chronic hepatitis C virus infection. *JAMA Neurology*, *76*(9), 1019–1027. https://doi.org/10.1001/jamaneurol.2019.1368.

Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., et al. (2020). Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *The Lancet. Neurology*, *19*(11), 919–929. https://doi.org/10.1016/S1474-4422(20)30308-2.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., et al. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature Neuroscience*, *24*(2), 168–175. https://doi.org/10.1038/s41593-020-00758-5.

Meng, L., Shen, L., & Ji, H. F. (2019). Impact of infection on risk of Parkinson's disease: A quantitative assessment of case-control and cohort studies. *Journal of Neurovirology*, *25*(2), 221–228. https://doi.org/10.1007/s13365-018-0707-4.

Mönkemüller, K., Fry, L., & Rickes, S. (2020). COVID-19, coronavirus, SARS-CoV-2 and the small bowel. *Revista Española de Enfermedades Digestivas*, *112*(5), 383–388. https://doi.org/10.17235/reed.2020.7137/2020.

Mpekoulis, G., Frakolaki, E., Taka, S., Ioannidis, A., Vassiliou, A. G., Kalliampakou, K. I., et al. (2021). Alteration of L-dopa decarboxylase expression in SARS-CoV-2 infection and its association with the interferon-inducible ACE2 isoform. *PLoS One*, *16*(6), e0253458. https://doi.org/10.1371/journal.pone.0253458.

Mukerji, S. S., & Solomon, I. H. (2021). What can we learn from brain autopsies in COVID-19? *Neuroscience Letters*, *742*, 135528. https://doi.org/10.1016/j.neulet.2020.135528.

Murray, R. S., Brown, B., Brian, D., & Cabirac, G. F. (1992). Detection of coronavirus RNA and antigen in multiple sclerosis brain. *Annals of Neurology*, *31*(5), 525–533. https://doi.org/10.1002/ana.410310511.

Nataf, S. (2020). An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *Journal of Medical Virology*, *92*(10), 1743–1744. https://doi.org/10.1002/jmv.25826.

Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., & Perlman, S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of Virology*, *82*(15), 7264–7275. https://doi.org/10.1128/jvi.00737-08.

Ousseiran, Z. H., Fares, Y., & Chamoun, W. T. (2021). Neurological manifestations of COVID-19: A systematic review and detailed comprehension. *The International Journal of Neuroscience*, *1-16*. https://doi.org/10.1080/00207454.2021.1973000.

Pavlov V.A. and Tracey K.J., 2012. The vagus nerve and the inflammatory reflex—Linking immunity and metabolism. *Nature Reviews Endocrinology*, *8*(12), 743–754. doi: 10.1038/nrendo.2012.189. PMID: 23169440; PMCID: PMC4082307.

Pellegrini, L., Albecka, A., Mallery, D. L., Kellner, M. J., Paul, D., Carter, A. P., et al. (2020). SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. *Cell Stem Cell*, *27*(6), 951–961.e955. https://doi.org/10.1016/j.stem.2020.10.001.

Pezzini, A., & Padovani, A. (2020). Lifting the mask on neurological manifestations of COVID-19. *Nature Reviews Neurology*, *16*(11), 636–644. https://doi.org/10.1038/s41582-020-0398-3.

Politi, L. S., Salsano, E., & Grimaldi, M. (2020). Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurology*, 77(8), 1028–1029. https://doi.org/10.1001/jamaneurol.2020.2125.

Porzionato, A., Stocco, E., Emmi, A., Contran, M., Macchi, V., Riccetti, S., et al. (2021). Hypopharyngeal ulcers in COVID-19: Histopathological and virological analyses - a case report. *Frontiers in Immunology*, *12*, 676828. https://doi.org/10.3389/fimmu.2021.676828.

Porzionato, A., Emmi, A., Contran, M., Stocco, E., Riccetti, S., Sinigaglia, A., et al. (2021). Case report: The carotid body in COVID-19: Histopathological and virological analyses of an autopsy case series. *Frontiers in Immunology*, *12*, 736529. https://doi.org/10.3389/fimmu.2021.736529.

Radnis, C., Qiu, S., Jhaveri, M., Da Silva, I., Szewka, A., & Koffman, L. (2020). Radiographic and clinical neurologic manifestations of COVID-19 related hypoxemia. *Journal of the Neurological Sciences*, *418*, 117119. https://doi.org/10.1016/j.jns.2020.117119.

Remmelink, M., De Mendonça, R., D'Haene, N., De Clercq, S., Verocq, C., Lebrun, L., et al. (2020). Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. *Critical Care*, *24*(1), 495. https://doi.org/10.1186/s13054-020-03218-5.

Sadasivan, S., Sharp, B., Schultz-Cherry, S., & Smeyne, R. J. (2017). Synergistic effects of influenza and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can be eliminated by the use of influenza therapeutics: Experimental evidence for the multi-hit hypothesis. *NPJ Parkinsons Disease*, *3*, 18. https://doi.org/10.1038/s41531-017-0019-z.

Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C. S. C., de Boer, H. H., et al. (2020). Viral presence and immunopathology in patients with lethal COVID-19: A prospective autopsy cohort study. *The Lancet Microbe*, *1*(7), e290–e299. https://doi.org/10.1016/S2666-5247(20)30144-0.

Schwabenland, M., Salié, H., Tanevski, J., Killmer, S., Lago, M. S., Schlaak, A. E., et al. (2021). Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions. *Immunity*, *54*(7), 1594–1610. https://doi.org/10.1016/j.immuni.2021.06.002.

Siddiqi, H. K., Libby, P., & Ridker, P. M. (2021). COVID-19 - A vascular disease. *Trends in Cardiovascular Medicine*, *31*(1), 1–5. https://doi.org/10.1016/j.tcm.2020.10.005.

Solomon, I. H., Normandin, E., Bhattacharyya, S., Mukerji, S. S., Keller, K., Ali, A. S., et al. (2020). Neuropathological features of Covid-19. *The New England Journal of Medicine*, *383*(10), 989–992. https://doi.org/10.1056/NEJMc2019373.

Sullivan, B. N., & Fischer, T. (2021). Age-associated neurological complications of COVID-19: A systematic review and meta-analysis. *Frontiers in Aging Neuroscience*, *13*, 653694. https://doi.org/10.3389/fnagi.2021.653694.

Sulzer, D. (2007). Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. *Trends in Neurosciences*, *30*(5), 244–250.

Sulzer, D., Antonini, A., Leta, V., Nordvig, A., Smeyne, R. J., Goldman, J. E., et al. (2020). COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside. *NPJ Parkinson's disease*, *6*, 18. https://doi.org/10.1038/s41531-020-00123-0.

Tandon, M., Kataria, S., Patel, J., Mehta, T. R., Daimee, M., Patel, V., et al. (2021). A comprehensive systematic review of CSF analysis that defines neurological manifestations of COVID-19. *International Journal of Infectious Diseases*, *104*, 390–397. https://doi.org/10.1016/j.ijid.2021.01.002.

Tang, Y.-W., Schmitz, J. E., Persing, D. H., & Stratton, C. W. (2020). Laboratory diagnosis of COVID-19: Current issues and challenges. *Journal of Clinical Microbiology*, *58*(6), e00512–e00520. https://doi.org/10.1128/JCM.00512-20.

Tanner, C. M., Ottman, R., Goldman, S. M., Ellenberg, J., Chan, P., Mayeux, R., et al. (1999). Parkinson disease in twins: An etiologic study. *JAMA*, *281*(4), 341–346. https://doi.org/10.1001/jama.281.4.341.

Thakur, K. T., Miller, E. H., Glendinning, M. D., Al-Dalahmah, O., Banu, M. A., Boehme, A. K., et al. (2021). COVID-19 neuropathology at Columbia University Irving medical center/New York presbyterian hospital. *Brain*, *144*(9), 2696–2708. https://doi.org/10.1093/brain/awab148.

Tsai, H. H., Liou, H. H., Muo, C. H., Lee, C. Z., Yen, R. F., & Kao, C. H. (2016). Hepatitis C virus infection as a risk factor for Parkinson disease: A nationwide cohort study. *Neurology*, *86*(9), 840–846. https://doi.org/10.1212/wnl.0000000000002307.

Tsivgoulis, G., Palaiodimou, L., Zand, R., Lioutas, V. A., Krogias, C., Katsanos, A. H., et al. (2020). COVID-19 and cerebrovascular diseases: A comprehensive overview. *Therapeutic Advances in Neurological Disorders*, *13*. https://doi.org/10.1177/1756286420978004.

Tsui, J. K., Calne, D. B., Wang, Y., Schulzer, M., & Marion, S. A. (1999). Occupational risk factors in Parkinson's disease. *Canadian Journal of Public Health. Revue Canadienne de Sante Publique*, *90*(5), 334–337. https://doi.org/10.1007/BF03404523.

Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., et al. (2020). Endothelial cell infection and endotheliitis in COVID-19. *Lancet*, *395*(10234), 1417–1418. https://doi.org/10.1016/s0140-6736(20)30937-5.

Verstrepen, K., Baisier, L., & De Cauwer, H. (2020). Neurological manifestations of COVID-19, SARS and MERS. *Acta Neurologica Belgica*, *120*(5), 1051–1060. https://doi.org/10.1007/s13760-020-01412-4.

Wan, D., Du, T., Hong, W., Chen, L., Que, H., Lu, S., et al. (2021). Neurological complications and infection mechanism of SARS-COV-2. *Signal Transduction and Targeted Therapy*, *6*(1), 406. https://doi.org/10.1038/s41392-021-00818-7.

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., et al. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*, *181*(4), 894–904.e899. https://doi.org/10.1016/j.cell.2020.03.045.

Williams, A., Branscome, H., Khatkar, P., Mensah, G. A., Al Sharif, S., Pinto, D. O., et al. (2021). A comprehensive review of COVID-19 biology, diagnostics, therapeutics, and disease impacting the central nervous system. *Journal of Neurovirology*, *27*(5), 667–690. https://doi.org/10.1007/s13365-021-00998-6.

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., et al. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China. Life Sciences*, *63*(3), 457–460. https://doi.org/10.1007/s11427-020-1637-5.

Yachou, Y., El Idrissi, A., Belapasov, V., & Ait Benali, S. (2020). Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: Understanding the neurological manifestations in COVID-19 patients. *Neurological Sciences*, *41*(10), 2657–2669. https://doi.org/10.1007/s10072-020-04575-3.

Yang, A. C., Kern, F., Losada, P. M., Agam, M. R., Maat, C. A., Schmartz, G. P., et al. (2021). Dysregulation of brain and choroid plexus cell types in severe COVID-19. *Nature*, *595*(7868), 565–571. https://doi.org/10.1038/s41586-021-03710-0.

Zazhytska, M., Kodra, A., Hoagland, D. A., Frere, J., Fullard, J. F., Shayya, H., et al. (2022). Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell*, *185*(6), 1052–1064.e1012. https://doi.org/10.1016/j.cell.2022.01.024.

Zhang, R., Wu, Y., Zhao, M., Liu, C., Zhou, L., Shen, S., et al. (2009). Role of HIF-1alpha in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *297*(4), L631–L640. https://doi.org/10.1152/ajplung.90415.2008.

Zhang, H., Kang, Z., Gong, H., Xu, D., Wang, J., Li, Z., 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*(6), 1010. https://doi.org/10.1136/gutjnl-2020-320953.

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 Neurology*, 77(8), 1018–1027. https://doi.org/10.1001/jamaneurol.2020.2065.