REVIEW

Covid-19 Infection and Parkinsonism: Is There a Link?

Rabia Bouali-Benazzouz, PhD,[1,2] and Abdelhamid Benazzouz, PhD[1,2*]

[1]*Université de Bordeaux, Institut des maladies neurodégénératives, Bordeaux, France*
[2]*CNRS, Institut des maladies neurodégénératives, Bordeaux, France*

ABSTRACT: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an opportunistic pathogen that infects the upper respiratory tract in humans and causes serious illness, including fatal pneumonia and neurological disorders. Several studies have reported that SARS-CoV-2 may worsen the symptoms of Parkinson's disease (PD), with the potential to increase mortality rates in patients with advanced disease. The potential risk of SARS-CoV-2 to induce PD has also been suggested because the virus can enter the brain, where it can trigger cellular processes involved in neurodegeneration. In this review, we will discuss the potential of SARS-CoV-2 to exacerbate and cause certain neurological disorders, including PD. We will then elucidate its impact on the brain while examining its pathways and mechanisms of action. © 2021 International Parkinson and Movement Disorder Society

Key Words: Covid-19; SARS-CoV-2; Parkinson's disease; parkinsonism; neurological disorders

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an opportunistic pathogen that infects the upper respiratory tract in humans and causes serious illness, including fatal pneumonia and neurological disorders. It belongs to the family of Coronaviridae that includes bat-derived viruses sharing highly homological sequences that cause clinical symptoms similar to those reported for SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infections.[1,2] SARS-CoV-2 is a large, enveloped, non-segmented, positive-sense RNA virus, and the seventh coronavirus known to infect humans.[3,4] It causes lethal pneumonia with severe acute respiratory distress syndrome.[5] SARS-CoV-2 shows some similarities with H1N1 influenza virus, especially regarding the activation of the immune system and alterations of epigenetic control mechanisms, which provide the first defense against viral infection.[6,7] Other similarities between SARS-CoV and H1N1 influenza virus infections also reside in modulations of the pathways involved in cellular aging, supporting the idea that SARS-CoV-2 infection may lead to accelerated aging phenotypes in affected tissues, including the brain, which may result in neurological disorders. A possible association of SARS-CoV-2 with the risk of Parkinson's disease (PD) has been suggested.[4] PD is characterized mainly by four cardinal motor symptoms (tremor, rigidity, akinesia, and postural instability), and also by non-motor symptoms.[8] These symptoms include depression, hyposmia, pain, anxiety, cognitive dysfunction, sleep disturbance, and constipation, which may appear even during the prodromal phase, before the clinical diagnosis of the disease.[9,10] Motor and non-motor symptoms are associated with the loss of dopaminergic neurons in the pars compacta of substantia nigra and the alteration of other neurotransmitter systems, including the noradrenergic and serotonergic systems.[11,12] Several studies investigating the impact of Covid-19 on PD have suggested that the symptoms in patients infected with SARS-CoV-2 worsened, that patients with advanced stage of PD were at increased risk for developing pneumonia problems, and that

***Correspondence to:** Dr. A. Benazzouz, Institut des maladies neurodégénératives, Centre Broca Nouvelle Aquitaine, Université de Bordeaux, 146 Rue Léoo-Saignat, 33076 Bordeaux Cédex 09, France; E-mail: abdelhamid.benazzouz@u-bordeaux.fr

Relevant conflict of interest/financial disclosures: Except for the annual financial support obtained from their two national (CNRS) and local (Université de Bordeaux) institutions, the authors have nothing to declare.

Funding agency: Centre national de la recherche scientifique (CNRS) and Université de Bordeaux.

Received: 22 January 2021; **Revised:** 18 May 2021; **Accepted:** 24 May 2021

Published online 8 June 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28680

hospitalized patients with PD and Covid-19 appeared to have a higher mortality rate.[13-17]

In this review, we will describe and discuss the potential risk of SARS-CoV-2 to cause and/or to exacerbate neurological disorders, including PD. Then, we will elucidate its impact on the brain while examining its entry pathways and action mechanisms.

SARS-CoV-2 and the Risk of Neurological Disorders

Despite numerous studies in favor of an attack on the central nervous system (CNS) by SARS-CoV-2, there are still many unknowns regarding the frequency or consequences of neuroinvasion. Furthermore, the CNS is not the primary organ affected; the investigation of neurological diseases in patients with Covid-19 is not systematic. A first case of meningitis/encephalitis associated with SARS-CoV-2 has been reported by Moriguchi and colleagues.[18] The patient manifested transient generalized seizures accompanied by unconsciousness, and brain magnetic resonance imaging showed hyperintense signal in the right medial temporal lobe, including the hippocampus. In line with this case report, acute and subacute neurological complications of SARS-CoV-2 infections have been reported in a large number of Covid-19 patients. Acute respiratory distress syndrome was associated with neurological signs in 84% of cases in a consecutive series of 58 patients.[19] The authors reported that agitation was present in 69%, dysexecutive syndrome in 36%, and corticospinal tract signs in 67% of patients. Systematic reviews reported other frequent neurological symptoms such as headaches, dizziness, hyposmia, hypogeusia encephalitis, and impaired consciousness.[20,21] Moreover, a retrospective study involving 214 Covid-19 patients found that 88% of the severe patients displayed acute cerebrovascular diseases and impaired consciousness.[22] Other neurological phenotypes have also been described in case reports, such as Guillain-Barré syndrome, paresthesias, polyneuropathy, epilepsy, and ischemic and hemorrhagic stroke.[23,24] Interestingly, several studies highlighted the exacerbation of neurological symptoms in Covid-19 patients with preexisting neurological disorders, which are considered as comorbidities associated with increased risk of death in Covid-19 patients.[25] Additionally, the association of worsening symptoms of Covid-19 in elderly people with neurological diseases are of concern for patients suffering from PD. Also, several reports discussed the possible association of SARS-CoV-2 not only with the exacerbation of the symptoms but also with the risk of causing PD.[26,27]

SARS-CoV-2 and PD

Although the link between Covid-19 and PD is particularly intriguing, several studies reported that PD patients are particularly susceptible to worsening symptoms with Covid-19.[14,15,28] This is supported by the fact that PD can compromise the respiratory system, as evidenced by the increased risk of pneumonia present in patients with advanced PD.[17] Interestingly, Kobylecki and colleagues[16] evaluated mortality rates and risk factors in hospitalized patients with idiopathic PD during the Covid-19 pandemic and they have shown that the combination of Covid-19 and PD can be fatal for patients. This was confirmed by other authors who found a high rate of mortality among PD patients.[28] Nevertheless, the risk of mortality depends on the severity of the symptoms, as Covid-19 risk morbidity and mortality in patients with mild to moderate PD does not differ from the general population.[29] Conversely, in a study of 141 patients with PD in Lombardy, Italy, the authors showed that 19 positive cases of SARS-CoV-2 showed a significant worsening of motor and nonmotor symptoms,[30] explaining that this clinical deterioration was due to both infection-related mechanisms and altered pharmacokinetics of dopaminergic therapy. In line with this study, a systematic review analyzing 26 articles comprising 2278 patients with preexisting neurological disorders and Covid-19 reported that SARS-CoV-2 induced an exacerbation of preexisting PD symptoms in 59% of infected patients.[31] Overall, all these studies suggest that patients with PD are at risk for a worse outcome with Covid-19, especially in advanced stages of the disease.

The occurrence of parkinsonism after viral infections has already been reported and well documented.[32] The first link between viruses and parkinsonism comes from the possible relationship between lethargic encephalitis and the Spanish flu of 1918. Post-mortem analysis of the brain of patients with parkinsonism showed signs of degeneration in the oculomotor nuclei and the substantia nigra. Subsequently, the risk of parkinsonism was multiplied by two or three times for people born between 1888 and 1924.[33] In addition, other viruses, including West Nile virus, herpes viruses, influenza A virus, and human immunodeficiency virus (HIV), have been associated with parkinsonism.[34,35] In the case of SARS-CoV-2, several arguments may support its possible induction of parkinsonism. Covid-19 patients develop hyposmia, which closely resembles one of the most prominent premotor symptoms of PD. Futhermore, in some cases (at least three reported in the literature), parkinsonism has been developed from 2 to 5 weeks after contracting SARS-CoV-2, which was at the origin of severe respiratory infection requiring hospitalization. Indeed, Méndez-Guerrero

and colleagues[36] were the first to report the case of a 58-year-old patient infected with SARS-CoV-2 who developed an asymmetric hypokinetic-rigid syndrome with mild resting and postural tremor, vertical occulomotor abnormalities, and hyposmia. The dopamine transporter single-photon emission computed tomography (DAT-SPECT) results demonstrated an asymmetric loss of dopamine fibers of the nigrostriatal pathway. Apomorphine, a dopamine agonist of D1 and D2 receptors, did not improve motor symptoms. However, this form of parkinsonism significantly improved spontaneously without any specific treatment. Another case report study[37] showed that after recovery from respiratory symptoms, a 35-year-old female patient developed sudden unilateral bradykinesia, moderate hyposmia, hypophonia, and generalized rigidity with decreased facial expression and gait disturbances. Levodopa/benserazide treatment significantly improved the motor symptoms and her Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) score decreased from 49 to 32. DAT scan examination showed a decrease in dopamine transporter (DAT) density on the left putamen. Furthermore, Cohen and colleagues[38] reported the case of a 45-year-old SARS-CoV-2-positive male patient who developed hypomimia, hypophonia, moderate rigidity, bradykinesia, tremor, and slightly slow gait. ^{18}F-Fluorodopa (^{18}F-FDOPA) positron emission tomography (PET) scan showed decreased ^{18}F-FDOPA uptake in the putamen. Treatment with pramipexole and biperiden resulted in an improvement of motor symptoms.

Authors of these case reports concluded that SARS-CoV-2 infection was responsible for the sudden parkinsonism, as (1) the patients were neurologically normal prior to the Covid-19; (2) they did not report a previous family history of PD; (3) their screening for genes related to PD, when done, were negative; (4) they are relatively young; and (5) they had no history of rapid eye movement sleep disorder and/or hyposmia, constipation, or depression prior to the infection. These non-motor symproms are known to appear in the prodromal phase of PD.[10]

In the absence of evidence of a causal link between SARS-CoV-2 infection and parkinsonism in these patients it is interesting to note that SARS-CoV-2 is able to enter the brain, where it can trigger the release of inflammatory mediators[39] known to play a role in specific neuronal degeneration. The role of infectious etiologies in the development of neurodegenerative diseases, such as Parkinsonism, has already been proposed.[40,41] However, the mechanisms by which a neurotropic pathogen can trigger neurodegeneration is still not clearly determined. One of the possibilities is that proinflammatory cytokines may stimulate neuronal expression of alpha-synuclein (α-Syn), the main protein component of Lewy bodies and Lewy neurites of dopaminergic neurons considered as a marker of PD pathology.[42] The involvement of α-Syn is supported by evidence in animal models showing that viral infections can trigger α-synucleinopathies.[43] Indeed, acute West Nile virus infection induced the aggregation of α-Syn, expressed by increased expression of this protein in primary neurons.[44] In the same way, these authors have also reported a dramatic increase in infectious viral particles of West Nile virus and Venezuelan equine encephalitis virus TC83 in the brains of α-Syn-knockout mice when compared to wild-type and heterozygote littermates. Accordingly, α-Syn-knockout mice exhibited significantly increased virus-induced mortality compared to α-Syn heterozygote or homozygote control mice. H5N1 infection in rodents also showed persistent microglial activation and abnormal phosphorylation of α-Syn, with loss of dopaminergic neurons in the substantia nigra.[40] Furthermore, infection of dopaminergic neurons with the H1N1 influenza virus resulted in the formation of α-Syn aggregates, but not of other proteins reported in other neurological pathologies, suggesting a highly selective nature of this process for PD.[41] These results allow to postulate that SARS-CoV-2 infection can trigger the aggregation mechanisms of α-Syn leading to cellular vulnerability and degeneration of dopaminergic neurons. This hypothesis has not been confirmed by a clinical study, as Blanco-Palmero and colleagues[45] did not find a significant change in serum α-Syn concentration in patients with Covid-19 and neurological disorders, compared with age- and sex-matched Covid-19 patients free of neurological symptoms and healthy controls.[45] However, the authors mentioned two limitations: (1) the study involved a small number of patients and (2) the serum sample analyzed in Covid-19 with neurological symptoms was extracted later in the course of the disease (31 days after symptom onset) than in Covid-19 patients without neurological symptoms (12 days). Further clinical studies taking into account these two parameters, as well as experimental studies using SARS-CoV-2 infection animal models, are needed.

Potential of SARS-Cov-2 to Enter the Brain

The manifestation of PD and other neurological disorders as well as the exacerbation of neurological symptoms in Covid-19 patients is evidence in itself of the strong impact of SARS-CoV-2 on the CNS. An interaction of human SARS-CoV-2 with the CNS has been suggested,[46] as several acute brain disorders are associated with the neuroinvasive predisposition to coronaviruses, including SARS-CoV-1, MERS-CoV, HcoV229E, and HcoV-OC43.[47,48] Neurological

disorders may be caused by the virus during the acute phase of the infection and persist beyond recovery. The idea that SARS-CoV-2 has the ability to penetrate and infect the brain came from earlier studies which reported the presence of SARS-CoV-1 particles in the cerebrospinal fluid (CSF)[49] and in the brain, almost exclusively located in the neurons.[50,51] Using transgenic mice, several studies showed that intranasal injection of either SARS-CoV[52] or MERS-CoV[47] resulted in the penetration of these viruses into the brain through the olfactory nerves, which rapidly spread to some specific brain regions, including the thalamus and brainstem. Moreover, it has to be noted that in infected mice with low doses of MERS-CoV virus, particles were detected only in the brain, especially in the brainstem, but not in the lung, indicating that the infection in the brain was more critical for the high mortality of the infected mice.[47] More recently, the consequences of SARS-CoV-2 infection were examined in vivo by using transgenic mice expressing human angiotensin-converting enzyme 2 (ACE2)[53] supporting the neuroreplicative potential and lethal consequences of SARS-CoV-2 CNS infection in mice. A possible link with PD has been shown after inoculation in mice with the influenza A neurovirulent virus. Thus, in the acute phase of viral infection, the virus was found in the substantia nigra, ventral tegmental area, and hippocampus, showing a selective and reproducible invasion of the virus in parenchymal tissues of the mouse brain.[54] These results are in favour of virus-induced parkinsonism with neurotropic properties, preferentially targeting the dopaminergic neurons of the substantia nigra.

Based on the high level of gene sequence similarity between SARS-CoV and SARS-CoV-2 (around 80%)[55] and the fact that a large number of patients with Covid-19 developed neurological disorders, it is logical to infer that SARS-CoV-2 has a significant potential to enter the CNS. Similar to other coronaviruses, SARS-CoV-2, as SARS-CoVs, uses mainly the same ACE2 receptor to enter the target cells.[56,57] SARS-CoV-2 infects cells through the interaction between its spike glycoprotein (S) and ACE2 receptor. Protein S is composed of two subunits S1 and S2, with S1 facilitating viral attachment to the ACE2 receptor, and S2 being required for membrane fusion.[56,57] For this interaction, protein S must be cleaved by transmembrane serine protease (TMPRSS2).[58,57] Cells expressing both ACE2 and TMPRSS2 are more susceptible to SARS-CoV-2 infection.[59] ACE2 receptor is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells, and small intestine cells.[60,61] Nuclear expression of ACE2 was also found in the brain, in both excitatory and inhibitory neurons, and also in astrocytes, oligodendrocytes, and endothelial cells in human middle temporal gyrus and posterior cingulate cortex.[21,62] In addition, ACE2 receptor is also present in the cardiorespiratory centers in the brain stem, the cerebral cortex, the posterior hypothalamic area, as well as the striatum and dopamine neurons of the substantia nigra.[63,64] The presence of ACE2 receptor in striatum and substantia nigra, as well as its co-expression with dopamine decarboxylase,[65] an enzyme converting L-dopa to dopamine, supports the involvement of SARS-CoV-2 in the pathophysiology of PD induced by viral infection.

The neuroinvasive propensity of SARS CoV-2 was also reported when the virus was found in the CSF and/or in the brain tissue of infected patients, providing strong evidence of neurotropism.[66,67] Indeed, while in some Covid-19 patients with encephalitis or demyelinating disease reverse transcription polymerase chain reaction (RT-PCR) showed the presence of SARS-CoV-2 in CSF samples,[18,68] other studies failed to detect the virus in the CSF in their cases.[23,69,70] However, Meinhardt and colleagues[39] reported the presence of intact coronavirus particles in the olfactory mucosa, using in situ hybridization, and SARS-CoV-2 RNA and spike protein within the CNS using immunohistochemistry and RT-PCR approaches. In only a few Covid-19 autopsy cases (3/24), the cerebellum was positive for SARS-CoV-2. The same authors reported that disease duration inversely correlated with the amount of detectable SARS-CoV-2 RNA in the CNS, with high SARS-CoV-2 RNA levels found in individuals with Covid-19 who had relatively short disease duration, whereas individuals with prolonged Covid-19 disease typically had low RNA load. Interestingly, another post-mortem anatomo-pathological study investigating the brain tissue of 43 patients who died after Covid-19 reported the presence of SARS-CoV-2 in the brain of 53% of patients.[71] The authors also reported new territorial ischemic lesions in 14% of patients, astrogliosis in different regions of the brain in 86% of patients, and meningeal cytotoxic T cell infiltration in 79% of patients. Microglia activation and cytotoxic T cell infiltration was more pronounced in the brainstem and cerebellum. Together, these observations suggest that severe acute respiratory syndrome of Covid-19 may be associated with the penetration of SARS-CoV-2 into the brain, causing worsening of symptoms and causing neurological disorders.[64] SARS-CoV-2 was also present in the brainstem, which is a respiratory and cardiovascular control center, suggesting the potential of the virus to play a role in the respiratory failure of some Covid-19 patients.[72,73]

Entry Pathways of SARS-CoV-2 into the Brain

The neurotropism of respiratory viruses has been demonstrated, and several studies argued that SARS-CoV-2

could infiltrate the brain either directly through the olfactory nerve and/or via a hematogenous route.

Entry Through the Olfactory Nerve

Preclinical studies, using mouse models expressing human ACE2 infected by intranasal inoculation with SARS CoV-2, have reported the presence of the virus in the brain.[74,75] However, nasal infection SARS CoV-2 in a non-human primate did not identify CoV-2 antigens in the brain.[76] Although these contrasting data in animal models, a recent interesting post-mortem study has explored the pathway entry of SARS-CoV-2 into the brain using in situ hybridization and immunohistochemical staining techniques to detect viral RNA and protein.[39] The authors reported the presence of SARS-CoV-2 S protein in the cytoplasm of endothelial cells and coronavirus particles together with SARS-CoV-2 RNA in the olfactory mucosa and brain areas receiving olfactory tract projections. This study suggested that SARS-CoV-2 neuroinvasion occurred via axonal transport, thus explaining why in some Covid-19 patients neurological symptoms may occur. Additionally, ACE2 has been shown to be expressed in support cells, stem cells, and perivascular cells in mouse, non-human primate, and human olfactory mucosa, suggesting that non-neuronal pathways may also play a role.[58] Interestingly, Meinhart and colleagues[39] have also shown the presence of SARS-CoV-2 RNA in the cerebellum, a brain region that has no direct connection with the olfactory mucosa. This result argued that axonal transport is not the only route of viral entry into the brain, and proposed that SARS-CoV-2 in the CNS endothelium might facilitate vascular damage and allow the virus to spread more widely to other brain regions.

Entry Through the Blood–Brain Barrier

Infection caused by viruses that induce neurological disorders may be associated with a disruption of the blood–brain barrier (BBB). This disruption is due to virus replication in cerebral microvascular endothelial cells causing the degradation of tightly bound proteins[77,78] In addition, post-mortem examination of the brain of a patient with Covid-19 showed that SARS-CoV-2 was present in cerebral microvascular endothelial cells and frontal lobe nerve tissue.[69] Furthermore, in a prospective cross-sectional study of 102 Covid-19 patients that were PCR-positive for SARS-CoV-2, 50% of the patients with severe neurological symptoms had BBB disruption and elevated interleukin levels in CSF.[79] Accordingly, Bellon and colleagues also showed BBB leakage in 58% of the 31 Covid-19 patients with neurological complications.[80] Taken together, these findings suggest that SARS-CoV-2 can damage and cross the BBB and once inside the brain can lead to neurological complications.

Conclusions

Overall, in this review we have examined the potential of SARS-CoV-2 to enter the brain primarily via the nasal route, but other routes may also be considered. From this, it is clearly established that the virus enters the brain, explaining the neurological disorders observed in a number of Covid-19 patients. Regarding the possibility of SARS-Cov-2 inducing PD, despite the pertinent observations, one limitation resides in the small number of cases of parkinsonism that have developed after Covid-19 infection reported in the literature. To gain in vivo relevance for that, the direct link between SARS-CoV-2 infection and the development of PD needs further explorative preclinical and clinical studies. Given the extent of the current Covid-19 pandemic and the high transmissibility of the SARS-CoV-2 virus, the association between this pandemic and PD raises concerns about the potential long-term effects of the virus on the CNS. In our opinion, although it is too early to elucidate the long-term side effects of SARS-CoV-2 infection, the background obtained with other respiratory viruses suggests that SARS-CoV-2 might induce permanent sequelae in the CNS by means of different mechanisms. ■

Acknowledgment: This work was supported by the University of Bordeaux, and the French National Centre for Scientific Research provided infrastructural support.

References

1. Hu B, Zeng L-P, Yang X-L, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog 2017;13(11):e1006698.
2. Luk HKH, Li X, Fung J, Lau SKP, Woo PCY. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. Infect Genet Evol 2019;71:21–30.
3. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and Sources of Endemic Human Coronaviruses. Adv Virus Res 2018;100:163–188. https://doi.org/10.1016/bs.aivir.2018.01.001
4. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: at the crossroad between aging and neurodegeneration. Mov Disord 2020;35(5):716–720.
5. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382(13):1199–1207.
6. Menachery VD, Eisfeld AJ, Schäfer A, et al. Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. mBio 2014;5(3): e01174–e01114.
7. Hui KPY, Cheung M-C, Perera RAPM, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. Lancet Respir Med 2020;8(7): 687–695.
8. Ehringer H, Hornykiewicz O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Klin Wochenschr 1960; 38:1236–1239.

9. Chaudhuri KR, Schapira AHV. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009;8(5):464–474.
10. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18(7):435–450.
11. Delaville C, Deurwaerdère PD, Benazzouz A. Noradrenaline and Parkinson's disease. Front Syst Neurosci 2011;5:31.
12. Blanchet PJ, Brefel-Courbon C. Chronic pain and pain processing in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 2018;87(Pt B):200–206.
13. Tan E-K, Albanese A, Kr C, et al. Adapting to post-COVID19 research in Parkinson's disease: lessons from a multinational experience. Parkinsonism Relat Disord 2020;82:146–149. https://doi.org/10.1016/j.parkreldis.2020.10.009
14. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. Mov Disord 2020;35(6):905–908. https://doi.org/10.1002/mds.28104
15. Hainque E, Grabli D. Rapid worsening in Parkinson's disease may hide COVID-19 infection. Parkinsonism Relat Disord 2020;75:126–127.
16. Kobylecki C, Jones T, Lim CK, Miller C, Thomson AM. Phenomenology and outcomes of in-patients with Parkinson's disease during the coronavirus disease 2019 pandemic. Mov Disord 2020;35(8):1295–1296.
17. Goh K-H, Acharyya S, Ng SY-E, et al. Risk and prognostic factors for pneumonia and choking amongst Parkinson's disease patients with dysphagia. Parkinsonism Relat Disord 2016;29:30–34.
18. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis 2020;94:55–58.
19. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020;382(23):2268–2270.
20. Abdullahi A, Candan SA, Abba MA, et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front Neurol 2020 Jun 26;11:687. https://doi.org/10.3389/fneur.2020.00687
21. Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. Front Neurol 2021 Jan 20;11:573095. https://doi.org/10.3389/fneur.2020.573095
22. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–690. https://doi.org/10.1001/jamaneurol.2020.1127
23. Al Saiegh F, Mouchtouris N, Khanna O, et al. Battle-tested guidelines and operational protocols for neurosurgical practice in times of a pandemic: lessons learned from COVID-19. World Neurosurg 2021;146:20–25.
24. Zhao J, Rudd A, Liu R. Challenges and potential solutions of stroke care during the coronavirus disease 2019 (COVID-19) outbreak. Stroke 2020;51(5):1356–1357.
25. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–436.
26. Brundin P, Nath A, Beckham JD. Is COVID-19 a perfect storm for Parkinson's disease? Trends Neurosci 2020;43(12):931–933.
27. Merello M, Bhatia KP, Obeso JA. SARS-CoV-2 and the risk of Parkinson's disease: facts and fantasy. Lancet Neurol 2020;20(2):94–95. https://doi.org/10.1016/S1474-4422(20)30442-7
28. Artusi CA, Romagnolo A, Imbalzano G, et al. COVID-19 in Parkinson's disease: report on prevalence and outcome. Parkinsonism Relat Disord 2020;80:7–9.
29. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson's disease patients living in Lombardy, Italy. Mov Disord 2020;35(7):1089–1093. https://doi.org/10.1002/mds.28176
30. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. Mov Disord 2020;35(8):1287–1292. https://doi.org/10.1002/mds.28170
31. Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: a systematic review. Clin Neurol Neurosurg 2021;200:106349.
32. Meng L, Shen L, Ji H-F. Impact of infection on risk of Parkinson's disease: a quantitative assessment of case-control and cohort studies. J Neurovirol 2019;25(2):221–228.
33. Ravenholt RT, Foege WH. 1918 Influenza, encephalitis lethargica, parkinsonism. Lancet 1982;2(8303):860–864.
34. Duvoisin RC, Yahr MD. Encephalitis and parkinsonism. Arch Neurol 1965;12:227–239.
35. Limphaibool N, Iwanowski P, Holstad MJV, Kobylarek D, Kozubski W. Infectious etiologies of parkinsonism: pathomechanisms and clinical implications. Front Neurol 2019;10:652.
36. Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. Neurology 2020;95(15):e2109–e2118.
37. Faber I, Brandão PRP, Menegatti F, de Carvalho Bispo DD, Maluf FB, Cardoso F. Coronavirus disease 2019 and parkinsonism: a non-post-encephalitic case. Mov Disord 2020;35(10):1721–1722.
38. Cohen ME, Eichel R, Steiner-Birmanns B, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. Lancet Neurol 2020;19(10):804–805.
39. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021;24(2):168–175.
40. Jang H, Boltz D, Sturm-Ramirez K, et al. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci U S A 2009;106(33):14063–14068.
41. Marreiros R, Müller-Schiffmann A, Trossbach SV, et al. Disruption of cellular proteostasis by H1N1 influenza a virus causes α-synuclein aggregation. Proc Natl Acad Sci U S A 2020;117(12):6741–6751.
42. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 1997;276(5321):2045–2047.
43. Tulisiak CT, Mercado G, Peelaerts W, Brundin L, Brundin P. Can infections trigger alpha-synucleinopathies? Prog Mol Biol Transl Sci 2019;168:299–322.
44. Beatman EL, Massey A, Shives KD, et al. Alpha-synuclein expression restricts RNA viral infections in the brain. J Virol 2015;90(6):2767–2782.
45. Blanco-Palmero VA, Azcárate-Díaz FJ, Ruiz-Ortiz M, et al. Serum and CSF alpha-synuclein levels do not change in COVID-19 patients with neurological symptoms. J Neurol 2021;19:1–9. https://doi.org/10.1007/s00415-021-10444-6
46. Li Z, Liu T, Yang N, et al. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. Front Med 2020;14(5):533–541. https://doi.org/10.1007/s11684-020-0786-5
47. Li K, Wohlford-Lenane C, Perlman S, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J Infect Dis 2016;213(5):712–722.
48. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol 2018 Aug 16;92(17):e00404-18. https://doi.org/10.1128/JVI.00404-18
49. Lau K-K, Yu W-C, Chu C-M, Lau S-T, Sheng B, Yuen K-Y. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004;10(2):342–344.
50. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004;203(2):622–630.
51. Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin Infect Dis 2005;41(8):1089–1096.

52. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008;82(15):7264–7275.

53. Song E, Zhang C, Israelow B, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med 2021 Mar 1;218(3): e20202135. https://doi.org/10.1084/jem.20202135.

54. Takahachi M, Yamada T, Nakajima S, Nakajima K, Yamamoto T, Okada H. The substantia nigra is a major target for neurovirulent influenza a virus. J Exp Med 1995;181(6):2161–2169.

55. Wang H, Li X, Li T, et al. The genetic sequence, origin, and diagnosis of SARS-CoV-2. Eur J Clin Microbiol Infect Dis 2020;39(9): 1629–1635.

56. Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell 2020;78(4):779–784.e5.

57. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–280.e8.

58. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020 Jul 31;6(31):eabc5801. https://doi.org/10.1126/sciadv.abc5801.

59. Han AY, Mukdad L, Long JL, Lopez IA. Anosmia in COVID-19: mechanisms and significance. Chem Senses 2020;17:bjaa040. https://doi.org/10.1093/chemse/bjaa040

60. Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000;87(5):E1–9.

61. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203(2):631–637.

62. Khan S, Gomes J. Neuropathogenesis of SARS-CoV-2 infection. Elife 2020;9:e59136. https://doi.org/10.7554/eLife.59136

63. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 2007;292(1): R373–381.

64. Rodriguez-Perez AI, Garrido-Gil P, Pedrosa MA, et al. Angiotensin type 2 receptors: role in aging and neuroinflammation in the substantia nigra. Brain Behav Immun 2020;87:256–271.

65. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. J Med Virol 2020; 92(10):1743–1744. https://doi.org/10.1002/jmv.25826

66. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 2020;383(6): 590–592.

67. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of Covid-19. N Engl J Med 2020;383(10):989–992.

68. Domingues RB, Mendes-Correa MC, de Moura Leite FBV, et al. First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. J Neurol 2020;267 (11):3154–3156.

69. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 2020;92(7):699–702.

70. Yin R, Feng W, Wang T, et al. Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. J Med Virol 2020;92(10):1782–1784.

71. Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 2020;19(11):919–929.

72. Khan S, Ali A, Siddique R, Nabi G. Novel coronavirus is putting the whole world on alert. J Hosp Infect 2020;104(3):252–253.

73. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Nerosci 2020;11 (7):995–998.

74. Jiang R-D, Liu M-Q, Chen Y, et al. Pathogenesis of SARS-CoV-2 in transgenic mice expressing human angiotensin-converting enzyme 2. Cell 2020;182(1):50–58.e8. https://doi.org/10.1016/j.cell.2020.05.027

75. Sun S-H, Chen Q, Gu H-J, et al. A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host Microbe 2020;28(1):124–133.e4. https://doi.org/10.1016/j.chom.2020.05.020

76. Munster VJ, Feldmann F, Williamson BN, et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature 2020;585 (7824):268–272.

77. Leda AR, Bertrand L, Andras IE, El-Hage N, Nair M, Toborek M. Selective disruption of the blood–brain barrier by Zika virus. Front Microbiol. 2019;10:2158.

78. Chiu C-F, Chu L-W, Liao I-C, et al. The mechanism of the Zika virus crossing the placental barrier and the blood-brain barrier. Front Microbiol 2020;11:214.

79. Fleischer M, Köhrmann M, Dolff S, et al. Observational cohort study of neurological involvement among patients with SARS-CoV-2 infection. Ther Adv Neurol Disord 2021;14: 1756286421993701.

80. Bellon M, Schweblin C, Lambeng N, et al. Cerebrospinal fluid features in SARS-CoV-2 RT-PCR positive patients. Clin Infect Dis 2020 Aug 8;ciaa1165. https://doi.org/10.1093/cid/ciaa1165