Opinion Piece

Studies on inflammation and stroke provide clues to pathomechanism of central nervous system involvement in COVID-19

Ádám Dénes[1], Stuart M. Allan[2], Tibor Hortobágyi[3,4], Craig J. Smith[5]

[1] *Laboratory of Neuroimmunology, Institute of Experimental Medicine, Szigony u. 43. 1083, Budapest, Hungary*
[2] *Division of Neuroscience and Experimental Psychology, Lydia Becker Institute of Immunology and Inflammation, The University of Manchester, Manchester Academic Health Science Centre, AV Hill Building, Manchester, M13 9PT, UK*
[3] *Department of Pathology, Faculty of Medicine, University of Szeged, Szeged, Hungary*
[4] *MTA-DE Cerebrovascular and Neurodegenerative Research Group, Department of Neurology, University of Debrecen, Debrecen, Hungary*
[5] *Division of Cardiovascular Sciences, Lydia Becker Institute of Immunology and Inflammation, The University of Manchester, Manchester Academic Health Science Centre, Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, M6 8HD, UK*

Corresponding author:
Ádám Dénes · Laboratory of Neuroimmunology · Institute of Experimental Medicine · Szigony u. 43. 1083 · Budapest · Hungary
denesa@koki.hu

Submitted: 26 May 2020 · Accepted: 28 May 2020 · Copyedited by: Calixto-Hope G Lucas, Jr. · Published: 05 June 2020

Keywords: COVID-19, SARS-CoV-2, Neuro-COVID, Stroke, Neuroinflammation, Neuropathology

Recent data, including a number of controversial findings from clinical COVID-19 studies, have initiated an intense debate regarding central nervous system (CNS) involvement in SARS-CoV-2 infection-associated pathologies and overall outcomes. In our opinion, involvement of the brain may be an important contributor to the highly complex pathophysiology caused by SARS-CoV-2 and lessons from studies on stroke and systemic inflammation provide important clues.

Numerous CNS symptoms, including loss of smell and taste, headache, dizziness, nausea, seizures and respiratory distress have been reported in COVID-19. Several neurological syndromes, such as stroke, encephalitis, epilepsy, and Guillain-Barre syndrome have been associated with COVID-19. More recently, large-vessel occlusive stroke has been described in younger patients without typical COVID-19 symptoms[1-3]. In addition, history of stroke is associated with increased severity of COVID-19[4]. These observations highlight the brain as an important target of this multiorgan disease. While neuroinvasion of SARS-CoV-2 has been associated with cerebral thrombosis, hemorrhagic infarction, demyelinating lesions and encephalopathy (termed as Neuro-COVID)[5,6], it has also been suggested that some respiratory symptoms in patients with COVID-19 could indicate neurological involvement[7]. Post-mortem examination of a series of patients with positive polymerase chain reaction testing for COVID-19 in pleural effusions revealed negative testing in all cerebrospinal fluid (CSF) samples along with no signs of encephalitis or CNS vasculitis[8]. This data may suggest that brain involvement in COVID-19 does not

play a major role in the disease pathogenesis. However, it appears difficult to draw firm conclusions from these observations. SARS-CoV-2 might not be detectable in the CSF due to low viral load, increased clearance, or the sensitivity of detection[5], while macroscopic analysis may not be sufficient to reveal the presence of infection in the brain tissue. Nevertheless, other arguments also indicate that neurological symptoms reported to date may be nonspecific and not necessarily imply CNS disease, while respiratory failure alone does not suggest CNS invasion by SARS-CoV-2[9]. However, in the absence of comprehensive neuropathological analysis, the extent and anatomical distribution of SARS-CoV-2 infection in the CNS remain unanswered. The robust inflammatory and prothrombotic response directly and indirectly affecting the CNS could explain some of the major neurological complications, which may be complemented by effects of possible SARS-CoV-2 infection in the brain.

Coronaviruses have long been recognised as potentially neurovirulent microorganisms[10]. Neuroinvasiveness of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), has been previously reported with pronounced infection in brainstem nuclei involved in respiratory and cardiovascular control[2,11]. Based on these data, SARS-CoV-2 might also reach the CNS via multiple routes. In viraemia, SARS-CoV-2 binds to the angiotensin-converting enzyme-2 (ACE2) receptor on the endothelium and, after crossing the blood-brain barrier (BBB), also binds to neurons expressing the receptor[12]. One of the currently available case reports with post-mortem neuropathology limited to electron microscopic examination in a frontal lobe sample demonstrates the virus in endothelial cells with features suggestive of transit of the virus towards the neuropil, and neuronal 'viral-like' particles in cytoplasmic vacuoles[13]. Via the olfactory route, the virus infects the olfactory epithelium, enters the nervous system across the cribriform plate through axons of olfactory bulb neurons, and then infects the sustentacular cells that maintain the integrity of olfactory sensory neurons. SARS-CoV-2 may also enter and spread via the cerebral lymphatic (glymphatic) drainage system since the virus can infect the endothelial cells of the olfactory lymphatic system which connect to the brain[12,14-16]. In addition, similar to herpesviruses or the avian influenza virus, SARS-CoV-2 could reach the brain via peripheral nerves, possibly via retrograde transport and trans-synaptic spread[17-19]. Deficient systemic immune response due to older age, chronic disease or immunosuppressive therapy, altered ACE2 expression in diabetic or hypertensive patients, cerebrovascular disease (major risk factors for COVID-19-associated mortality)[1,4], as well as vascular inflammation or impaired blood-brain barrier (BBB) function in aged or comorbid patients could also increase the risk and severity of infection. If CNS infection occurs, the outcome largely depends on the ability of the CNS immune system to control the spread of the virus. Studies on neurotropic virus infection suggest that microglia, the main inflammatory cells of the CNS, are important in controlling both the spread of the virus and shaping the cerebral inflammatory response. This key role of microglia has been experimentally demonstrated in coronavirus, herpesvirus, Theiler's virus and vesicular stomatitis virus infection among others[20-24]. Importantly, lack of normal microglial function not only increases viral spread in the brain, but is also associated with markedly worsened neurological symptoms (motor function deficits, neuronal injury, brain oedema, seizures, etc.) and increased mortality in animal models[20-24]. Microglial phenotype is heavily influenced by age, comorbidities and systemic inflammation[25]. Therefore, it is likely that compromised microglial function is an important contributor to poor outcome in Neuro-COVID, especially if brain areas involved in respiratory, cardiovascular and neuroendocrine control are affected by SARS-CoV-2. Effective antiviral drug delivery through the BBB may therefore be important in the management of neurological complications.

Irrespective of whether CNS SARS-CoV-2 infection occurs, the cerebral effects of systemic inflammation associated with "cytokine storm" and prothrombotic state have profound impact on outcome in severe COVID-19 cases. High serum levels of inflammatory cytokines, such as IL-6, predict poor outcome[26] and may contribute to cardiac- and respiratory arrest, coma and multiorgan failure through complex mechanisms that include microcirculatory deficits, hypotension, oedema and thrombosis. Circulating inflammatory cytokines stimulate the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis with major impact on blood pressure and flow, respiration and neuroendocrine function. The autonomic nervous system and HPA axis also play an important role in the regulation of immune cell responses, cytokine production, cell trafficking and cell death via both humoral and neural mechanisms. The sustained increase in serum adrenaline, noradrenaline and cortisol levels due to prolonged autonomic and HPA axis activation eventually lead to dysregulation of inflammatory responses. This, in line with excessive cytokine production, results in insufficient elimination of infectious agents. The lymphopenia due to apoptosis and impaired lymphopoiesis shifts immune cell balance towards excessive monocyte and granulocyte load, further increasing the production myeloid cell-derived proinflammatory cytokines.

The excessive systemic inflammatory response also contributes to the neurological complications via direct

and indirect actions. Findings from clinical and experimental stroke studies with preceding or post-stroke infection may help to shed light on the mechanisms of COVID-19-related neurological impairment. Stroke in apparently healthy young- and middle-aged people with rapid formation of thrombi in the cerebral circulation and high mortality of older patients with chronic inflammatory disease collectively suggest a high impact of altered coagulation in patients with COVID-19[27,28]. Infections in general (e.g. seasonal flu) increase stroke incidence[29]. As known from studies of viral and bacterial sepsis and from comorbid models of stroke, increased systemic inflammatory burden promotes vascular inflammation, platelet activation and alters coagulation cascades, leading to a procoagulant state leading to thrombosis and disseminated intravascular coagulation. Such coagulopathy, predictive of worse clinical outcome, has been reported in COVID-19[30,31]. This promotes thrombus formation in both veins and arteries – a known feature of severe COVID-19 with thromboembolic complications reported in around one third of infected patients[32]. The cerebrovascular endothelial cells have particularly high sensitivity to proinflammatory cytokines and SARS-CoV-2 infection could further boost the expression of adhesion molecules and increase vascular permeability. Brain injury and mortality are generally far more severe in patients with additional stroke risk factors (e.g. in obese, diabetic, hypertensive patients or after infection), similarly to that seen in experimental stroke models. As an example, localized infection of the lungs by influenza virus or Streptococcus pneumoniae leads to marked increases in circulating proinflammatory cytokines, endothelial activation (indicated by increased levels of adhesion molecules) and platelet aggregation. These infection-driven changes are associated with augmented brain inflammation and leukocyte recruitment, leading to increased neuronal injury and worse neurological outcome[33-35]. Targeted blockade of proinflammatory cytokines (e.g. IL-6, IL-1 or TNF) or platelet-endothelial interactions attenuated infection-induced brain injury in experimental models[33,34,36-38], while the potential efficacy of IL-6 receptor antagonist Tocilizumab to reduce mortality in severe COVID-19 cases has been suggested[39].

Recent reports have described patients with ischaemic stroke complicating COVID-19 infection, often manifesting as large-vessel infarcts occurring in multiple territories and associated with features of prothrombotic coagulopathy[3,40,41]. However, these small case series may not be representative of wider clinical practice, and no causal relationship has yet been established between COVID-19 infection and stroke. Other mechanisms may also be relevant, such as destabilisation of atheromatous plaques resulting in thrombosis and cerebral atheroembolism, atrial fibrillation in critically ill patients causing thromboembolism of cardiac origin, or haemorrhage secondary to microangiopathy and cerebral vasculitis. Importantly, patients may also acquire SARS-CoV-2 infection following stroke. Suppression of both innate and adaptive immune response is well-documented after stroke, driven by autonomic nervous system failure and activation of the HPA axis, which could exacerbate subclinical infection, or increase susceptibility to nosocomial infection.

An important issue to address is whether neurological manifestations (reported in up to one third of cases with different severity of infection[1,42]) result from systemic effects on the brain, direct CNS infection by SARS-CoV-2, or both, and if the latter is a major contributor to COVID-19-related severe illness and mortality. Firm conclusions cannot be drawn at this stage due to limited data availability, but it is likely that the impact of CNS-related effects on disease outcome is considerable. Most neurological manifestations appear to occur early in the illness, preceding severe respiratory distress and the need for mechanical ventilation, while several patients are admitted to the hospital merely based on neurologic manifestation with no respiratory symptoms[1]. At this time, data are largely from single case reports. For example, occurrence of neurological symptoms such as fever, anosmia, dysgeusia, headache and possible seizure in line with respiratory distress and severe ventilator asynchronies were found in a patient where autopsy later confirmed the presence of SARS-CoV-2 infection in the brain. Findings included widespread tissue damage involving the neurons, glia, nerve axons, and myelin sheath, progressively more severe from the olfactory nerve to the gyrus rectus and to the brainstem[43]. A recent report showed that after positive diagnosis for SARS-CoV-2, a patient developed complete anosmia and dysgeusia, with MRI showing signs of bilateral olfactory bulb oedema, followed by normalization of both sensory symptoms and MRI signal by day 14[44]. Another report found that 44% of patients admitted to the intensive care unit with COVID-19 and neurological symptoms showed CNS abnormalities on MRI, which included cortical (frontal, parietal, occipital, temporal, insular) and deep white matter FLAIR signal abnormalities, in the absence of SARS-CoV-2 in the CSF (50% of cases tested). Thus, while focal neuropathologies appear to be frequent in severe cases, the extent of associated brain infection remains unclear presently. Of note, the incidence of epileptiform discharges, seizure-like events and new onset encephalopathy is more than two-fold higher in acutely ill COVID-19 patients with neurological symptoms compared to non-infected patients, but it is not known if this is through direct or indirect actions on the CNS[45]. While SARS-CoV-2 infection shares many similari-

ties with bacterial sepsis, the inflammatory response was considered more modest (e.g. lower IL-6 levels), and progressive and profound suppression of adaptive immunity was noted in COVID-19 relative to sepsis[46]. Therefore, further studies are required to assess the nature of systemic inflammatory changes and their impact on neurological symptoms and disease outcome.

In conclusion, the available evidence strongly indicates that the brain is an important target of SARS-CoV-2 and the impact of its brain-related pathophysiology on survival and outcome in COVID-19 is substantial. While diagnostic efforts and research studies to investigate the presence of infection in the brain and to reveal the mechanisms of both central and systemic inflammation in COVID-19 are necessary, lessons from previous work on infection, stroke and systemic inflammation should be considered. Regarding the clinical management of COVID-19 patients, immune modulatory therapies are attractive candidates. In this respect it will be intriguing to learn the outcomes of ongoing clinical trials of anti-cytokine therapies, including anakinra (IL-1 receptor antagonist) and Tocilizumab (IL-6 receptor antibody).

References

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*. 2020;e201127. doi:10.1001/jamaneurol.2020.1127
2. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*. 2020; S0889-1591(20)30357-3. doi:10.1016/j.bbi.2020.03.031
3. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhrim S, Fifi JT. Large-vessel stroke as a presenting feature of COVID-19 in the young. *The New England Journal of Medicine*. 2020;382:e60. doi:10.1056/NEJMc2009787
4. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): A pooled analysis of published literature. *International Journal of Stroke*. 2020;1747493020921664. doi:10.1177/1747493020921664
5. Panciani PP, Saraceno G, Zanin L, Renisi G, Signorini L, Battaglia L, Fontanella MM. SARS-CoV-2: "Three-steps" infection model and CSF diagnostic implication. *Brain, Behavior, and Immunity*. 2020 May 5, doi: 10.1016/j.bbi.2020.05.002
6. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, Fontanella MM. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochirurgica*. 2020 May 4;1-4. doi: 10.1007/s00701-020-04374-x
7. Recasens BB, Llorens JMM, Sevilla JJR, Rubio MA. Lack of dyspnea in patients with COVID-19: Another neurological conundrum? *European Journal of Neurology*. 2020 Apr 17, doi: 10.1111/ene.14265
8. Schaller T, Hirschbuhl K, Burkhardt K, Braun G, Trepel M, Markl B, Claus R. Postmortem examination of patients with COVID-19. *JAMA*. May 21, 2020. doi:10.1001/jama.2020.8907
9. Turtle L. Respiratory failure alone does not suggest central nervous system invasion by SARS-CoV-2. *Journal of Medical Virology*. 04, April 2020. https://doi.org/10.1002/jmv.25828
10. Desforges M, Le Coupanec A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: Potential neurovirulent agents in humans. *Advances in Experimental Medicine and Biology*. 2014;807:75-96
11. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology*. 2020;10.1002/jmv.25728. doi:10.1002/jmv.25728
12. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-CoV-2 invade the brain? Translational lessons from animal models. *European Journal of Neurology*. 2020;10.1111/ene.14277. doi:10.1111/ene.14277
13. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, Sordillo EM, Fowkes M. Central nervous system involvement by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2). *Journal of Medical Virology*. 2020;10.1002/jmv.25915. doi:10.1002/jmv.25915
14. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418
15. Bostancikliogl M. SARS-CoV-2 entry and spread in the lymphatic drainage system of the brain. *Brain, Behavior, and Immunity*. 2020; doi: 10.1016/j.bbi.2020.04.080
16. Leon Fodoulian JT, Daniel Rossier, Basile N. Landis, Alan Carleton, Ivan Rodriguez. Sars-cov-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium.*bioRxiv2020.03.31.013268;doi: https://doi.org/10.1101/2020.03.31.013268*
17. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dube M, Talbot PJ. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? *Viruses*. 2019;12
18. Matsuda K, Shibata T, Sakoda Y, Kida H, Kimura T, Ochiai K, Umemura T. In vitro demonstration of neural transmission of avian influenza a virus. *The Journal of General Virology*. 2005;86:1131-1139
19. Csonka T, Szepesi R, Bidiga L, Peter M, Klekner A, Hutoczky G, Csiba L, Mehes G, Hortobagyi T. [the diagnosis of herpes encephalitis--a case-based update]. *Ideggyogyaszati Szemle*. 2013;66:337-342
20. Reinert LS, Lopusna K, Winther H, Sun C, Thomsen MK, Nandakumar R, Mogensen TH, Meyer M, Vaegter C, Nyengaard JR, Fitzgerald KA, Paludan SR. Sensing of HSV-1 by the cgas-sting pathway in microglia orchestrates antiviral defence in the cns. *Nature Communications*. 2016;7:13348
21. Fekete R, Cserep C, Lenart N, Toth K, Orsolits B, Martinecz B, Mehes E, Szabo B, Nemeth V, Gonci B, Sperlagh B, Boldogkoi Z, Kittel A, Baranyi M, Ferenczi S, Kovacs K, Szalay G, Rozsa B, Webb C, Kovacs GG, Hortobagyi T, West BL, Kornyei Z, Denes A.

Microglia control the spread of neurotropic virus infection via P2Y12 signalling and recruit monocytes through P2Y12-independent mechanisms. *Acta Neuropathologica*. 2018;136:461-482

22. Drokhlyansky E, Goz Ayturk D, Soh TK, Chrenek R, O'Loughlin E, Madore C, Butovsky O, Cepko CL. The brain parenchyma has a type I interferon response that can limit virus spread. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;114:E95-E104
23. Wheeler DL, Sariol A, Meyerholz DK, Perlman S. Microglia are required for protection against lethal coronavirus encephalitis in mice. *The Journal of Clinical Investigation*. 2018;128:931-943
24. Waltl I, Kaufer C, Gerhauser I, Chhatbar C, Ghita L, Kalinke U, Loscher W. Microglia have a protective role in viral encephalitis-induced seizure development and hippocampal damage. *Brain, Behavior, and Immunity*. 2018;74:186-204
25. Dubbelaar ML, Kracht L, Eggen BJL, Boddeke E. The kaleidoscope of microglial phenotypes. *Frontiers in Immunology*. 2018;9:1753
26. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science*. 2020;368:473-474
27. Lippi G, Wong J, Henry BM. Hypertension and its severity or mortality in coronavirus disease 2019 (COVID-19): A pooled analysis. *Polish Archives of Internal Medicine*. 2020;130:304-309. doi:10.20452/pamw.152722020
28. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. *American Journal of Hematology*. 2020;10.1002/ajh.25829. doi:10.1002/ajh.25829
29. Miller EC, Elkind MS. Infection and stroke: An update on recent progress. *Current Neurology and Neuroscience Reports*. 2016;16:2
30. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet*. 2020;395:1054-1062
31. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020;18:844-847
32. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*. 2020;S0049-3848(20)30120-1. doi:10.1016/j.thromres.2020.04.013
33. Denes A, Pradillo JM, Drake C, Sharp A, Warn P, Murray KN, Rohit B, Dockrell DH, Chamberlain J, Casbolt H, Francis S, Martinecz B, Nieswandt B, Rothwell NJ, Allan SM. Streptococcus pneumoniae worsens cerebral ischemia via interleukin 1 and platelet glycoprotein Ib-alpha. *Annals of Neurology*. 2014;75:670-683
34. Denes A, Humphreys N, Lane TE, Grencis R, Rothwell N. Chronic systemic infection exacerbates ischemic brain damage via a CCL5 (regulated on activation, normal t-cell expressed and secreted)-mediated proinflammatory response in mice. *The Journal of Neuroscience*. 2010;30:10086-10095
35. Muhammad S, Haasbach E, Kotchourko M, Strigli A, Krenz A, Ridder DA, Vogel AB, Marti HH, Al-Abed Y, Planz O, Schwaninger M. Influenza virus infection aggravates stroke outcome. *Stroke*. 2011;42:783-791
36. McCann SK, Cramond F, Macleod MR, Sena ES. Systematic review and meta-analysis of the efficacy of interleukin-1 receptor antagonist in animal models of stroke: An update. *Translational Stroke Research*. 2016;7:395-406
37. Bonetti NR, Diaz-Canestro C, Liberale L, Crucet M, Akhmedov A, Merlini M, Reiner MF, Gobbato S, Stivala S, Kollias G, Ruschitzka F, Luscher TF, Beer JH, Camici GG. Tumour necrosis factor-alpha inhibition improves stroke outcome in a mouse model of rheumatoid arthritis. *Scientific Reports*. 2019;9:2173
38. Lambertsen KL, Finsen B, Clausen BH. Post-stroke inflammation-target or tool for therapy? *Acta Neuropathologica*. 2019;137:693-714
39. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6r) antagonist tocilizumab may be the key to reduce the mortality. *International Journal of Antimicrobial Agents*. 2020:105954
40. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *The New England Journal of Medicine*. 2020;382:e38
41. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humphries F, Jager HR, Losseff NA, Perry RJ, Shah S, Simister RJ, Turner D, Chandratheva A, Werring DJ. Characteristics of ischaemic stroke associated with COVID-19. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2020;jnnp-2020-323586. doi:10.1136/jnnp-2020-323586
42. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, Kaya Y, Yildirim D, Tuzuner F, Yildirim MS, Ozluk E, Gucyetmez B, Karaarslan E, Koyluoglu I, Demirel Kaya HS, Mammadov O, Kisa Ozdemir I, Afsar N, Citci Yalcinkaya B, Rasimoglu S, Guduk DE, Kedir Jima A, Ilksoz A, Ersoz V, Yonca Eren M, Celtik N, Arslan S, Korkmazer B, Dincer SS, Gulek E, Dikmen I, Yazici M, Unsal S, Ljama T, Demirel I, Ayyildiz A, Kesimci I, Bolsoy Deveci S, Tutuncu M, Kizilkilic O, Telci L, Zengin R, Dincer A, Akinci IO, Kocer N. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology*. 2020:201697
43. Bulfamante G, Chiumello D, Canevini MP, Priori A, Mazzanti M, Centanni S, Felisati G. First ultrastructural autoptic findings of SARS-CoV-2 in olfactory pathways and brainstem. *Minerva Anestesiologica*. 2020;10.23736/S0375-9393.20.14772-2.
44. Laurendon T, Radulesco T, Mugnier J, Gerault M, Chagnaud C, El Ahmadi AA, Varoquaux A. Bilateral transient olfactory bulbs edema during COVID-19-related anosmia. *Neurology*. May 22, 2020; 10.1212/WNL.0000000000009850
45. Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Gursky J, Hanumanthu R, Hung C, Molinero I, Khodakivska O, Legatt AD, Patel P, Rosengard J, Rubens E, Sugrue W, Yozawitz E, Mehler MF, Ballaban-Gil K, Haut SR, Moshé SL, Boro A. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. *Epilepsia Open*. 2020; https://doi.org/10.1002/epi4.12399
46. Remy KE, Brakenridge SC, Francois B, Daix T, Deutschman CS, Monneret G, Jeannet R, Laterre PF, Hotchkiss RS, Moldawer LL. Immunotherapies for COVID-19: lessons learned from sepsis. *Lancet Respiratory Medicine*. 2020;S2213-2600(20)30217-4. doi:10.1016/S2213-2600(20)30217-4