



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial commentary: The nervous system, COVID-19 and cerebrovascular complications: A strange riddle of the time

Madhavan Nampoothiri

Department of Pharmacology, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India

At the outset of the coronavirus disease 2019 (COVID-19) pandemic, a series of vascular and thromboembolic manifestations were reported. This gave rise to enumerable findings on the risk of stroke and other cerebrovascular problems. Cerebral venous sinus thrombosis, cerebrovascular vasculopathy, ischemic stroke and intracerebral hemorrhage have all been reported as possible complications. Further, following administration of the modified adenovirus-based SARS-CoV-2 (Severe acute respiratory coronavirus 2) vaccine, cases of cerebrovascular complications have been reported [1]. At present, greater emphasis has been given to the role of the nervous system in COVID-19 [2].

Post-acute sequel of COVID-19 such as hematologic, cardiovascular and neuropsychiatric complications are “long COVID” with a complex clinical picture characterized by fatigue, sleep disturbances, cognitive impairment, palpitations, thromboembolism, chronic kidney disease and neuropsychiatric disturbances. Indeed, neuropathological data highlighted the distribution of angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine protease (TMPRSS2) in the endothelial cells of cerebral capillaries, oligodendrocytes, astrocytes, motor cortex, hippocampus and brain stem involved in autonomic function [3]. The entry of SARS-CoV-2 into the brain through cerebrospinal fluid (CSF), olfactory, trigeminal nerve, gastrointestinal and hematogenous routes have been reported as robust correlates of long term complications in COVID-19 [4]. After entering into the central nervous system (CNS), structural proteins particularly the spike proteins facilitate the spike attachment and host membrane fusion. It is worth noting that the envelope, nucleocapsid and membrane proteins make SARS-CoV-2 proliferation and infection spread considerably easier than expected [5].

Endothelial injury, the release of proinflammatory cytokines, complement activation, hypoxia and platelet-dependent mechanisms seem to be linked with the risk of thrombotic problems in the post-acute COVID-19 phase [6]. The coagulopathy caused by COVID-19 is associated with an inflammatory state. Interestingly, cytokine storm may disrupt the blood-brain barrier aiding viral entry [6]. The pro-inflammatory cytokine exposure in astrocytes stimulates the expression of proinflammatory genes that cause neuroinflammation and neurodegeneration [7]. It should be em-

phasized that the incidence of thrombotic complications as a long-term consequence of COVID-19 might be correlated to the severity and duration of hyperinflammatory state. The pathophysiology of vascular injury in COVID-19 is still a wild chasm. Nevertheless, ACE-2 dependent and independent mechanism and spike protein-mediated direct platelet activation has been identified [8].

Pericytes in the brain are specialized cells that are essential in maintaining the blood-brain barrier (BBB) and neurovascular coupling via cerebral blood flow (CBF) modulation. The SARS-CoV-2 S protein disrupts brain pericytes' vascular and immunological regulatory functions, which could explain vascular-mediated brain injury [9]. Yet, regardless of the increasing advances in neuroimaging techniques a unique interpretation of the neurological manifestations supporting such an intense degree of interaction between inflammation and COVID-19 associated coagulopathy is far from being consistent. Thus, additional measures are required to measure this and to further investigate the patient's neurological status.

Recently, in parallel to the accumulative insight into the neuropsychiatric consequence of COVID-19, several studies have specified the role of inflammation in the brain [10,11]. The occurrence of inflammatory lesions in the brain parenchyma has been observed in COVID-19 associated encephalitis [12]. Cellular and humoral immune response to the SARS-CoV-2 virus is misguided to the host nerve tissue resulting in Guillain-Barre syndrome. Neurological disorders such as meningitis, meningoencephalitis, seizures, anxiety, depression and cranial neuropathy are fairly widespread and pose a serious difficulty in COVID-19 patient treatment [13]. Cognitive dysfunction causing fluctuations in learning and memory, concentration, thinking, language and judgment has been observed as a long-term neurological sequel of COVID-19 [14]. A great number of reports display a heightened risk of neurodegenerative disorders in COVID-19 patients [15]. In this interesting framework of neural circuit involved in cognition, the relations of SARS-CoV-2 has given neuroscientists a wide matter of investigation. Furthermore, the evidence of damage to the hippocampus and striatum, olfactory dysfunction, autonomic impairment and neuroimaging brain changes in COVID-19 patients supports the idea of neurological disorders as an initial manifestation of a multifaceted neurodegenerative process. Evidence of neuroinflammation in SARS-CoV-2 infection suggests the role of NLRP3 activation and release of pro-inflammatory cytokines [16]. The role of NLRP3 in various chronic neurological diseases have been established [17]. Taken together, a broad spectrum of neurologic manifestations including cerebrovas-

DOI of original article: [10.1016/j.tcm.2022.04.004](https://doi.org/10.1016/j.tcm.2022.04.004)

E-mail address: madhavan.ng@manipal.edu

<https://doi.org/10.1016/j.tcm.2022.05.001>

1050-1738/© 2022 Elsevier Inc. All rights reserved.

cular complications remains to be studied and an integrated approach to explore the pathophysiology of long-term complications of COVID-19 is warranted in the upcoming years.

References

- [1] Krzywicka K, Heldner MR, Sanchez van Kammen M, Van Haaps T, Hiltunen S, Silvis SM, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European medicines agency. *Eur J Neurol* 2021;28(11):3656–62.
- [2] Hingorani KS, Bhadola S, Cervantes-Arslanian AM. COVID-19 and the brain. *Trends Cardiovasc Med* 2022 In press.
- [3] Qi J, Zhou Y, Hua J, Zhang L, Bian J, Liu B, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to SARS-CoV-2 infection. *Int J Environ Res Public Health* 2021;18(1):284.
- [4] Khatoon F, Prasad K, Kumar V. COVID-19 associated nervous system manifestations. *Sleep Med* 2021;91:231–6.
- [5] Deore BJ, Tran KA, Andrews AM, Ramirez SH, Galie PA. SARS-CoV-2 spike protein disrupts blood–brain barrier integrity via RhoA activation. *J Neuroimmune Pharmacol* 2021;16(4):722–8.
- [6] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med* 2021;27(4):601–15.
- [7] Chowdhury B, Sharma A, Satarker S, Mudgal J, Nampoothiri M. Dialogue between neuroinflammation and neurodegenerative diseases in COVID-19. *J Environ Pathol Toxicol Oncol* 2021;40(3):37–49.
- [8] Magro CM, Mulvey J, Kubiak J, Mikhail S, Suster D, Crowson AN, et al. Severe COVID-19: a multifaceted viral vasculopathy syndrome. *Ann Diagn Pathol* 2021;50:151645.
- [9] Khaddaj-Mallat R, Aldib N, Bernard M, Paquette AS, Ferreira A, Lecordier S. SARS-CoV-2 deregulates the vascular and immune functions of brain pericytes via spike protein. *Neurobiol Dis* 2021;161:105561.
- [10] Pratt J, Lester E, Parker R. Could SARS-CoV-2 cause tauopathy? *Lancet Neurol* 2021;20(7):506.
- [11] Cardenas G, Fragoso G, Scitutto E. Neuroinflammation in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection: pathogenesis and clinical manifestations. *Curr Opin Pharmacol* 2022;63:102181.
- [12] Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immune* 2020;88:945.
- [13] Satarker S, Nampoothiri M. Involvement of the nervous system in COVID-19: the bell should toll in the brain. *Life Sci* 2020;262:118568.
- [14] Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH, Gunning FM. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacol* 2021;46(13):2235–40.
- [15] Singh H, Singh A, Khan AA, Gupta V. Immune mediating molecules and pathogenesis of COVID-19-associated neurological disease. *Microb Pathog* 2021;158:105023.
- [16] Wang H, Lu J, Zhao X, Qin R, Song K, Xu Y, et al. Alzheimer's disease in elderly COVID-19 patients: potential mechanisms and preventive measures. *Neurol Sci* 2021;42:4913–30.
- [17] Kinra M, Nampoothiri M, Arora D, Mudgal J. Reviewing the importance of TL-R-NLRP3-pyroptosis pathway and mechanism of experimental NLRP3 inflammasome inhibitors. *Scand J Immunol* 2022;95(2):13124.