



Correlating Biochemical and Structural Changes in the Brain with Clinical Features in COVID-19

Abdul Mannan Baig*

Cite This: <https://doi.org/10.1021/acschemneuro.2c00164>

Read Online

ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: With emerging reports of the deleterious effects of SARS-CoV-2 reflecting as neurological deficits in COVID-19, the biochemical and morphological changes it casts on the brain are also being investigated. This is an important niche of research as it is expected to predict and relate the neurological clinical features in the acute phase and chronic syndromic forms of COVID-19. Here debated are the biochemical and structural changes that can be related to the neurological manifestations in COVID-19.

KEYWORDS: SARS-CoV-2, COVID-19, neurological deficit, imaging, CNS damage, long-COVID, long-haulers

INTRODUCTION

About 2 years ago, in the year 2020, reports and published literature appeared that heralded the neurological deficits caused by SARS-CoV-2 based on clinical outcomes in patients admitted to hospitals in Wuhan, China.^{1,2} The anatomical structures and known pathways of the SARS-CoV-2 to the brain were predicted¹ based on the clinical features in the patients who have been admitted to the hospitals in Wuhan, China. No gross or microscopic findings had been presented as a shred of evidence, at that time, to support the pathways or specific zones of the brain involved in the cases of fatalities resulting from COVID-19 early during the pandemic. Also early in the pandemic, there was reluctance and delays in acknowledging direct neuronal injury caused by SARS-CoV-2 in COVID-19. The biopsy finding after autopsy of the brain and spinal cord coupled with neuroimaging data that has been accumulated now clearly elucidates the neurological damages in COVID-19 (Figure 1). Relating the morphological findings obtained from the biopsies performed during autopsies in COVID-19 and long-COVID to the clinical feature exhibited by the patients during the ongoing pandemic is much needed to gauge the severity of the neurological damages that are caused by SARS-CoV-2 in COVID-19. Apart from direct damage caused by SARS-CoV-2 (Figure 1A1,B), neuronal injury caused by inflammation, hypoxia, and cytokines was also implicated in the causation of neuronal damage (Figure 1A1). Although neuroimaging and other noninvasive modalities could be of diagnostic and prognostic significance in neuro-COVID, it is, however, important to mention here that clinical features in neuro-COVID can be exhibited even in the absence of morphological abnormalities seen on imaging (Figure 1C). As biochemical events are known to precede morphological change during cellular injury, the patients with COVID-19 may exhibit neurological features ahead of alterations detected in imaging modalities like CT scans and MRI reported recently.³ Keeping the latter in mind and with the wide range of clinical features in the COVID-19 and long-COVID patients, with the appearance

of normal to the near-normal brain and spinal cord scans (Figure 1C), there is a need to identify CSF biomarkers and serum markers (Figure 1, top-right panel), that can hint toward an ongoing neuronal injury. Additional diagnostic modalities like nerve conduction studies, PET scans, and thorough clinical examination should be brought into consideration to include or exclude the neurological deficits in symptomatic COVID-19 patients with features of neurological damage.

Susceptibility of the Neurons to Cellular Injury and Routes to the Brain. Among the tissues and organs of the human body, the neurons that are the building blocks of the human central nervous system (CNS), and glial cells, are sensitive cells that succumb easily to diverse factors capable of causing cell damage like hypoxia, extremes of pH, toxic chemicals, and infectious organisms including viruses. Also, unlike other human tissues where a cellular loss is compensated by regeneration of identical cells by the stem cells, the human CNS mostly is devoid of stem cells; therefore a neuronal loss is a permanent event and mostly is replaced by gliosis. Given the sensitivity of the neurons and glia to injurious influences, evolutionarily the CNS has built the blood–brain barrier (BBB) to protect itself from damaging influences. The toxin and microbes that enter the CNS can adopt routes that can bypass the BBB. Examples include nerve gases and parasite pathogens like *Naegleria fowleri*. In COVID-19 the SARS-CoV-2 has been shown⁵ to reach the brain via the cribriform plate of the ethmoid bone,^{1,4,5} bypassing the BBB (Figure 1 A).

Relating the Effects of Neuronal Injury to Syndromic Neuro-COVID. The knowledge of the functions of different areas of the brain has enabled us to relate the zone of neuronal

Received: March 11, 2022

Accepted: March 21, 2022

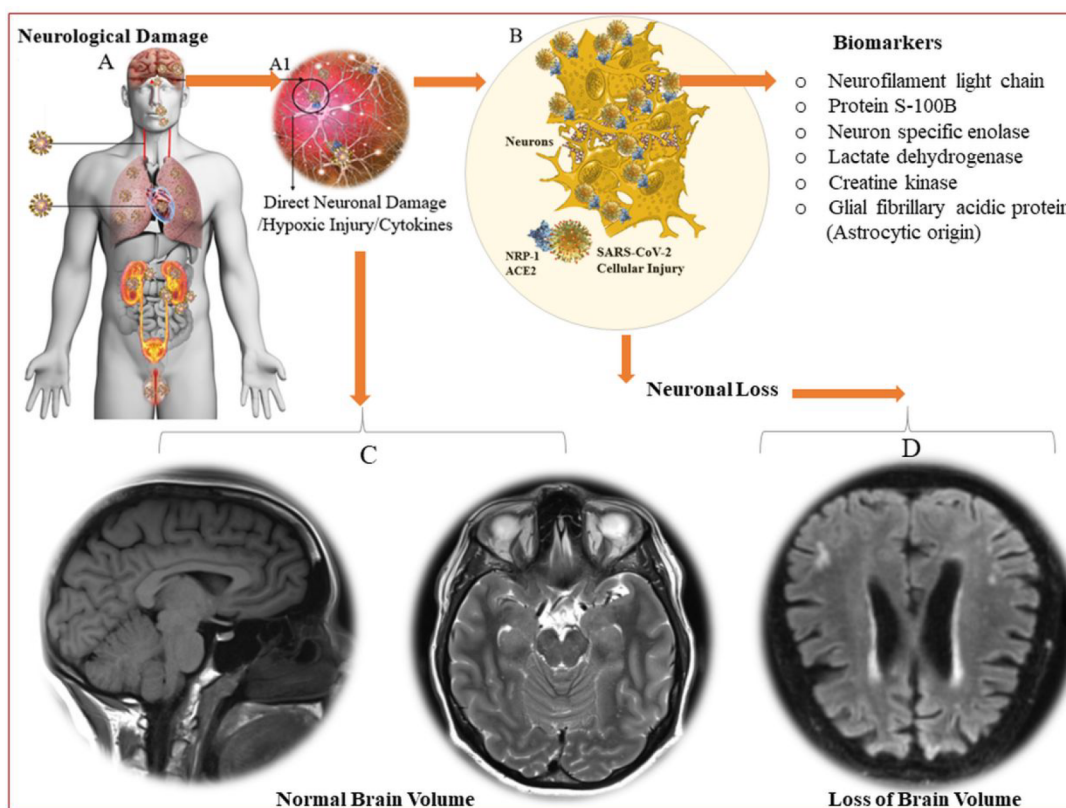


Figure 1. SARS-CoV-2 causes neurological damage via direct neuronal injury or inflammation (A1). Early neuronal damage (B) at the molecular level would not appear on brain scans (C). The release of chemicals in the CSF and blood can serve as a biomarker of neuronal injury (top-right). A thinning of the gray matter and widening of sulci (D) may appear after a considerable loss of neurons in COVID-19 and long-COVID.

damage to functional loss. In a patient who presents with signs and symptoms of neurological origin, a CT scan or MRI of a particular area of the brain can provide clues toward neuronal damages caused by either direct effects of the SARS-CoV-2^{1,5} or diverse factors like hypoxia, inflammation, or cytokine-mediated injury. This correlation is not possible when the damage is ongoing at the molecular level and the changes sufficient to document an abnormality on CT scan or MRI are yet to be developed (Figure 1 C), as has been the case with many patients with long-COVID in long-haulers who exhibit neurological features like “brain fog” and diminished cognitive functions.

Need for Investing in Biomedical Research in Neuro-COVID. To prevent damages to the neurons before they can cause fatality in COVID-19 or disability in long-COVID, it is important to invest in research that can identify biochemical markers (Figure 1, top-right panel) that can be a clue toward an ongoing neuro-COVID in either acute phase or chronic syndromic form of COVID-19 as in the case of long-haulers.⁵ Prevention of neuro-COVID by topical drug and vaccine delivery devices that can reduce the viral load in the nose⁵ is also needed. The research on COVID-19 and the recently emerging long-COVID patients is in its infancy, and a huge investment in research is expected to find a resolution in the form of neurotropic antiviral agents or anti-inflammatory drugs that can cross the BBB and reduce inflammation and cytokine-mediated neuronal damage in long-COVID and COVID-19.

DISCUSSION AND CONCLUSION

The neurological damages that have been reported in the current pandemic of COVID-19 are of concern not only because

the CNS involvement in COVID can cause mortalities more than the similar intensity of infection in any other organ or tissue but also because of the concern of the disabilities expected in the patients who survive the acute phase of COVID-19. The latter is not a prediction but a fact, as this has been seen in long-COVID and long-haulers⁵ that has now been recognized by WHO and CDC as a disease entity. Most of the patients with long-COVID are disabled due to particular or diffuse damage to the CNS as has been reported recently. After the first indication of the COVID-19 targeting the CNS via the nose, published in *ACS Chemical Neuroscience*, and the hints that the virus may opt for a pathway across the cribriform plate at the root of the nose to reach the olfactory pathways and brain,¹ the finding of mRNA of SARS-CoV-2 around the cribriform plate, olfactory bulb, and diverse regions of the brain⁴ should have alerted us to anticipate the neurological damages in COVID-19. Similarly, this viewpoint is drawing attention toward a wide range of neurological deficits caused by SARS-CoV-2 in long-haulers and long-COVID. Immediate investment in form of funding research by the healthcare regulating bodies is needed to minimize the incidence of neurological deficits in long-COVID syndrome. Early detection by identification of biomarkers that hint neurological damage in COVID-19 is needed. Though scan-related changes would prove to be of enormous value to study CNS damages in COVID-19,³ prevention of irreversible neuronal and glial damage long before the loss of brain mass leading to changes in CT and MRI could prove to be one of the ways to contain neuro-COVID during this pandemic.

AUTHOR INFORMATION

Corresponding Author

Abdul Mannan Baig – Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, Sindh 74800, Pakistan; orcid.org/0000-0003-0626-216X; Phone: +92-[0]333-2644-246; Email: abdul.mannan@aku.edu

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acschemneuro.2c00164>

Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

The author thanks the members of Long Covid-19 Foundation, U.K., for their discussions into diverse causes of long-COVID. This research has no funding resources.

REFERENCES

- (1) Baig, A. M.; 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. Neurosci.* **2020**, *11* (7), 995–998.
- (2) Li, Y. C.; Bai, W. Z.; Hashikawa, T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J. Med. Virol.* **2020**, *92*, 552.
- (3) Douaud, G.; Lee, S.; Alfaro-Almagro, F.; et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *medRxiv* **2022**, DOI: [10.1101/2021.06.11.21258690](https://doi.org/10.1101/2021.06.11.21258690), (preprint).
- (4) Meinhardt, J.; 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*, 168–175.
- (5) Baig, A. M. Counting the neurological cost of COVID-19. *Nat. Rev. Neurol.* **2022**, *18* (1), 5–6.