

Brain autopsies in fatal COVID-19 and postulated pathophysiology: more puzzling than a Rubik's cube

THE EDITOR

A little over century after the 1918 influenza pandemic, the world is witnessing another pandemic of similar magnitude, caused by SARS-CoV-2 and affecting nearly 215 countries. Although SARS-CoV-2 primarily affects the lungs, neurological presentations are being recognised with increasing frequency. Recently, Ellul and colleagues¹ have elaborated a spectrum of neurological diseases in 901 patients of COVID-19. Here, we describe three case series of brain autopsies^{2–4} that have revealed distinctly different pathologies, failing to explain the common pathobiological mechanism of central nervous system (CNS) involvement in severe COVID-19.

Solomon *et al*² reported histopathological changes in autopsies of 18 patients with COVID-19 from a teaching hospital. Gross inspection showed no changes suggestive of acute stroke, herniation or olfactory bulb damage. Microscopic examination revealed changes of acute hypoxia in the cerebrum and cerebellum in 100% of patients with COVID-19, with neuronal loss in various structures like cerebral cortex, hippocampus and cerebellar Purkinje cell layer. There were no findings of thrombosis or vasculitis. Focal leptomeningeal inflammation was reported in brain specimen of one patient with COVID-19. No histopathological changes were observed in the olfactory bulbs or tracts ruling out neuronal pathway of spread of SARS-CoV-2. Also, SARS-CoV-2 virus was not detected in the brain, suggesting indirect effect of SARS-CoV-2 in the brain of these patients.

Adult respiratory distress syndrome leading to respiratory failure is commonly seen in severe and critically ill patients with COVID-19 and can cause hypoxia in the brain. The latter may also occur due to direct invasion of the medullary cardiorespiratory centre by the virus.⁵ The SARS-CoV-2 can spread from the peripheral nerves of the respiratory network into the medulla

oblongata, where respiratory centre is regulated.⁵ Hypoxic brain leads to anaerobic metabolism in the brain cells resulting in lactic acid accumulation, which in turn, causes cerebral oedema, reduced blood flow and increased intracranial pressure.

In another series of postmortem analysis on six patients with COVID-19 reported by von Weyhern,³ CNS involvement occurred in form of pan-encephalitis, meningitis and brainstem damage. Surprisingly, authors observed no conspicuous endotheliitis in the brain. The authors suggested that these changes could not be attributed to severe hypoxia observed in critical COVID-19 cases.

One possible pathophysiological mechanism includes neuronal transport of SARS-CoV-2 by means of the olfactory pathway. The virus enters cerebrospinal fluid (CSF) and brain through olfactory nerve and bulb and can incite inflammatory as well as demyelinating reactions. Intense cytokine release during florid cytokine storm make blood–brain barrier more permeable, thereby facilitating entry of SARS-CoV-2 into the brain. In the brain, the virus can infect astrocytes and microglia and activate neuroinflammation through the release of various cytokines including tumour necrosis factor, cytokines and reactive oxygen species (ROS). It has been demonstrated that faecal viral shedding can occur up to 5 weeks following infection.⁶ The gut has high density of ACE-2 receptors in comparison to the lungs and thus is a potential site of virus entry. Subsequently, through the enteric nervous system, the virus may gain entry into the brain.

Hypercoagulability is a common pathobiological manifestation in severe and critical COVID-19 cases. The high concentration of cytokine milieu leads to activation of the coagulation cascade and suppression of the fibrinolytic system.⁷ Pulmonary and peripheral endothelialitis secondary to direct viral attack can also strongly activate the coagulation system by exposure of tissue factor. It has been postulated that antiphospholipid syndrome may also contribute to cerebral thrombosis.⁸ However, presence of antiphospholipid antibodies in COVID-19 should be cautiously interpreted.⁹

Schaller *et al*⁴ in 10 autopsies found specifically no signs of encephalitis or CNS vasculitis. Postmortem CSF samples tested negative for SARS-CoV-2 by reverse transcriptase PCR. Brain remained unaffected in these 10 patients with severe/critical COVID-19.

Possibly, SARS-CoV-2 can affect the brain through direct routes—haematogenous

and neuronal pathways and also by indirect mechanisms which include cytokine dysregulation, peripheral immune cell transmigration, neuroinflammation, postinfectious autoimmunity, hypercoagulability, etc. A very recent study¹⁰ also documented some of the above pathobiological mechanisms of CNS involvement in COVID-19.

The neuropathological changes in brain autopsies in fatal COVID-19 have proved to be more puzzling than a Rubik's Cube! Better understanding of CNS involvement in COVID-19 will evolve with correlation between pathological changes in brain autopsies, clinical manifestations and pathobiological mechanisms.

Sudhir Mehta¹,¹ Sudhir Bhandari,¹ Shaurya Mehta²

¹Department of Medicine, SMS Medical College (University Medical School), Jaipur, Rajasthan, India

²Department of Nephrology, Jaslok Hospital & Research Centre, Mumbai, Maharashtra, India

Correspondence to Professor Sudhir Mehta, Department of Medicine, SMS Medical College (University Medical School), Jaipur, Rajasthan 302004, India; s.mehta@hotmail.com

Handling editor Runjan Chetty.

Contributors All authors contributed equally to the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.



To cite Mehta S, Bhandari S, Mehta S. *J Clin Pathol* 2021;**74**:612–613.

Received 20 July 2020

Revised 11 August 2020

Accepted 13 August 2020

Published Online First 9 September 2020

J Clin Pathol 2021;**74**:612–613.

doi:10.1136/jclinpath-2020-206967

ORCID iD

Sudhir Mehta <http://orcid.org/0000-0003-2506-3174>

REFERENCES

- 1 Ellul MA, Benjamin L, Singh B, *et al*. Neurological associations of COVID-19. *Lancet Neurol* 2020;19:767–83.
- 2 Solomon IH, Normandin E, Bhattacharyya S, *et al*. Neuropathological features of Covid-19. *N Engl J Med Overseas Ed* 2020.

- 3 von Weyhern CH, Kaufmann I, Neff F, *et al.* Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet* 2020;395:e109.
- 4 Schaller T, Hirschtbühl K, Burkhardt K, *et al.* Postmortem examination of patients with COVID-19. *JAMA* 2020. doi:10.1001/jama.2020.8907. [Epub ahead of print: 21 May 2020].
- 5 Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020;92:552–5.
- 6 Wu Y, Guo C, Tang L, *et al.* Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020;5:434–5.
- 7 Cao W, Li T. COVID-19: towards understanding of pathogenesis. *Cell Res* 2020;30:367–9.
- 8 Zhang Y, Xiao M, Zhang S, *et al.* Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382:e38.
- 9 Mehta S, Bhandari S, Mehta S. Cautious interpretation of antiphospholipid antibodies in COVID-19. *Clin Chim Acta* 2020;509:166.
- 10 Varatharaj A, Thomas N, Ellul MA, *et al.* Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 2020. doi:10.1016/S2215-0366(20)30287-X. [Epub ahead of print: 25 Jun 2020].