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 colleagues[1] 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 study[10] 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 Mehta ,[1] **Sudhir Bhandari**,[1] **Shaurya Mehta**[2]

[1]Department of Medicine, SMS Medical College (University Medical School), Jaipur, Rajasthan, India
[2]Department 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.smehta@hotmail.com

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ORCID iD
Sudhir Mehta http://orcid.org/0000-0003-2506-3174

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