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 have elaborated a spectrum of neurological diseases in 901 patients of COVID-19. Here, we describe three case series of brain autopsies 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. 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 pathways to 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. Pulmonary and 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. However, presence of antiphospholipid antibodies in COVID-19 should be cautiously interpreted.

Schaller et al. 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 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.

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