Brain Fog: A Post-COVID-19 Sequelae? A Perspective

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Over the last two and half years, there have been about six million COVID-19 related deaths worldwide. However, till date, the relatively unexplored, often hidden, progressive deterioration of health of COVID-19 survivors has not been getting that much attention to the medical community, in part due to the slowness of the disease progression, together with the lack of standard tests to correctly diagnose the long-haul of SARS-CoV-2 in patients that might be causing dysfunctions in varieties of organs including the brain. Evidence suggests that many people have ongoing cognitive problems post-recovery from initial COVID-19 disease. Besides, people who have only mild COVID-19 symptoms can develop long-term recurring problems with attention, concentration, and memory known as “Brain Fog” that arise presumably due to post-COVID sequela (PCS)¹. In fact, brain fog²,³,⁴ can lead to long-term neurodegenerative diseases (ND) and advances the progression of existing ND or the onset of full-blown ND. The complexity of PCS in terms of wide range of symptoms makes its diagnosis challenging from other health related problems, and people may have a wide variety of similar PCS like symptoms that could come from other health problems. Although, brain MRI (Magnetic Resonance Imaging) and FDG PET (Fluorodeoxyglucose (FDG)-positron emission tomography) scans are often useful in detecting post-COVID brain damage. That said, the long-term course of these brain lesions and associated clinical symptoms in mild forms of COVID in patients is difficult to predict, till date. Therefore, it is critical to understand the detailed underlying mechanisms of PCS together with the development of brain fog in COVID-19 patients. Unfortunately, till now, a lack of understanding of this double-edged sword poses a significant risk to many of the COVID-19 patients who may eventually develop persistent brain fog long after the initial SARS-CoV-2 infections.

SARS-CoV-2 is often believed to penetrate the olfactory mucosa, causing loss of smell, although, conclusive evidence in favor of this is still lacking. Second, SARS-CoV-2 could penetrate blood-brain barrier (BBB)⁵ with the help of proinflammatory cytokines released into the blood circulation as a result of cytokine storm, leading to BBB instability and/or disruption and through SARS-CoV-2-infected monocytes present in the blood circulation using Trojan-horse mechanism-entering into brain to elicit brain disorders⁶ including brain fog. Third, SARS-CoV-2 could reach brain tissue via circumventricular organs that primarily act as a gatekeeper to regulate entry and exit of critical substances in the brain without disrupting BBB, and permit substances that do not normally cross the BBB to trigger changes in brain function. Thus, increased levels of proinflammatory cytokines such as interleukin-6, interleukin-10, and tumor necrosis factor-alpha (TNF-alpha) in the brain of SARS-CoV-2-infected patients can activate microglia⁷, resulting in phagocytosis of damaged cells, together with secretion of inflammatory mediators, including glutamate, quinoloi acids, complement proteins and TNF-alpha. Higher levels of glutamate in the brain...
along with upregulation of N-methyl-D-aspartate (NMDA) receptors by quinoloid acid impair learning ability, memory, and neuroplasticity, further causing hallucinations including other cognitive dysfunctions. Thus, neuroinflammation associated with PCS, even with mild form of infection, could be linked to hypometabolic lesions observed in some COVID-19 patients. Also, a significant longitudinal effect of SARS-CoV-2 in the brain was observed in COVID-19 patients with a reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus along with a greater reduction in global brain size. It is observed that grey matter brain reserve predicts executive functioning, especially in the older individuals. In addition, reduction in brain size can potentially affect the anatomy of executive functions arising from the critical parts of the brain such as prefrontal cortex, basal ganglia and thalamus. To further explore the underlying mechanisms of PCS, in an animal study, persistently impaired hippocampal neurogenesis, dysregulation of multi-lineage neural cells, and myelin loss were observed, concomitant with higher levels of cytokines/chemokines including CCL11 (C-C motif chemokine ligand 11) in the cerebrospinal fluid (CSF), resulting in activation of hippocampal microglial cells and impaired neurogenesis. Interestingly, humans with lasting cognitive symptoms have shown to exhibit elevated CCL11 levels following SARS-CoV-2 infections.

In spite of substantial amount of evidence for brain fog cases detected by imaging, and often behavioral studies in asymptomatic and symptomatic COVID-19 patients along with proposed underlying mechanisms, in many cases, test that determines objective cognition primarily reflects self-reported cognitive symptoms, could pose serious challenges in distinguishing negative cases from actual brain fog disease, especially in the early phase of its development. It is also not clear whether SARS-CoV-2 binds to neuronal cells through ACE2 (Angiotensin-converting enzyme 2) receptor via spike protein and can survive in the brain. Evidence of SARS-CoV-2’s presence in the CSF has been rare, although, there could be numerous other pathways by which neurotropism may occur, but exact mechanism is still lacking. Retrograde neuronal access via peripheral nerves, hematogenous transmission by directly infecting endothelial cells, and more recently, binding of envelope protein of SARS-CoV-2 to TLR2 (Toll-like receptor 2) in the CNS, are some of the well-hypothesized mechanisms for SARS-CoV-2’s putative entry into the CNS. Moreover, skepticism remains about whether SARS-CoV-2 stays latent in the body, especially in the immune-privileged sites such as brain, spinal cord and eyes, long after the initial infections, given the fact that a subset of people continues testing positive for the virus weeks or months after developing COVID-19 symptoms who could be potentially developing brain fog in the end. Importantly, it is largely unknown whether COVID-19 vaccines can erase the symptoms of PCS and prevent the development of brain fog. Lastly, many of the mechanistic studies are limited with the fact that fatigue and cognitive impairment could be the consequences of chronic stress and/or depression resulting from social and economic challenges of COVID-19 pandemic, rather than a direct effect of SARS-CoV-2 infections, in a fraction of PCS patients.

Taken together, the link between PCS and executive functions of the brain raises pertinent questions regarding patients’ long-term disease management. Future studies are needed to identify the critical risk factors including psychosocial stressors and discerning central mechanism(s) underlying cognitive dysfunctions associated with brain fog for newer pharmacological interventions including stem cell therapy, together with behavioral interventions for better rehabilitation of COVID-19 patients with brain fog to improve upon Disability-Adjusted Life Years (DALY) in tune with the Sustainable Development Goals.

References


