Acta Scientific Neurology (ISSN: 2582-1121)

Volume 4 Issue 11 November 2021

Short Communication

How COVID-19 Affects the Brain?

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Received: September 20, 2021

Published: October 21, 2021

Warping the 21st century into an intangible reality is the SARS-CoV-2 triggered COVID-19 pandemic. With its myriad presentations and indefinite modes of management, it continues to confound the world with an unparalleled medical, societal, and economic crisis [1,2]. Attracting particular attention is the way SARS-CoV-2 affects the human brain. With newer clinical and pre-clinical data revealing that the virus doesn't restrict itself to just the respiratory, gastrointestinal and cardiovascular systems, and well surpasses into the nervous system; various conjectural hypotheses have arisen [3]. Occurring independent of and unrelated to other systems, the Central Nervous System (CNS) implications are seen in almost 20-70% of the infected patients [4]. The evident neurotropism and neuro-invasion further complicates the already disruptive pandemic. How does the SARS-CoV-2 enter the brain? How does it infect the neurons? What is its contribution to the pathophysiology of the presentation of COVID-19 infection? Is it relevant to the present situation? And most protuberantly, what will the sequelae comprise?

Various pathways of entry into the CNS have been hypothesised, albeit lacking conclusive evidence. First, is through the olfactory pathway. Once in the nasal cavity, the virus infects the olfactory neurons in the olfactory epithelium, giving rise to the symptom of anosmia; eventually reaching the CNS through olfactory nerve. Dysgeusia may also be attributable to this, as olfactory pathway is one of the various stimuli relaying at the frontal lobe, responsible for gustation. The other pathways into the CNS are through circulation: via Circumventricular Organs (CVOs) into the brain, or through fenestrated capillaries into the Cerebral Spinal Fluid (CSF) [4,5]. Isolation of the virus from ocular fluids has also given rise to theories of eye-based transmission of the virus. The most important mode of access of SARS-CoV-2 into the CNS has been hypothesised to be through the Angiotensin-Converting Enzyme 2 (ACE-2) receptors [3,5]. Once attached to the ACE-2 receptors, the virus inflicts significant endothelial damage in cerebral capillaries, causing Blood Brain Barrier (BBB) disruption. SARS-CoV-2 protein has been isolated from brain vascular endothelium. In addition, there is abundant expression of ACE-2 receptors in neurons and microglia, especially in the medullary regions of cardiorespiratory control in the brain stem [3,4]. This gives rise to theories suggestive of a central origin of respiratory and cardiac failure in infected cases; which is supported by histopathologic findings of microglial nodules and phagocytosed neurons in the brain stem more than in the cortex and limbic structures [3-5].

SARS-CoV-2 infection, like other viral infections, leads to development of a cytokine storm, and most likely involve both cell-mediated and humoral immune responses [4,5]. Pro-inflammatory cytokines like IL-1, IL-6, IL-10, and TNF-α are secreted in large amounts. The levels of lymphocytes, eosinophils and monocytes are decreased, as against an increased neutrophil count which entirely attributes to the elevated leukocyte levels, and also results in an elevated Neutrophil to Lymphocyte Ratio (NLR). Biomarkers of infection, namely: procalcitonin, C-reactive Protein, Erythrocyte Sedimentation Rate, are also seen to be elevated [5].

The aforementioned events result in activation of microglia and astrocytes, which: phagocytose damaged cells, and cause further secretion of inflammatory mediators, such as glutamate, quinolinic acid, interleukins, complement proteins and TNF-α. Neuronal loss due to phagocytosis leads to region-specific and neurotransmitter-specific neurological sequelae. On the other hand, the excessive inflammatory mediators cause a spike in glutamate, as well as upregulation of NMDA receptors, which can be attributable to attention deficits, altered memory, hallucinations, and nightmares [4]. Systemic inflammation results in activation of the enzyme indolamine dioxygenase, which causes preferential metabolization of tryptophan to kynurenine over serotonin, pointing to the etiological basis of depressive disorder in patients with COVID-19 [4,5]. Interleukins, due to the dysregulation of Hypothalamic-Pituitary Adrenal (HPA) axis, and interferon-α due to its association with a decreased turnover of monoamine neurotransmitters particularly in the caudate and putamen, are also known to be correlated with depressive symptomatology [3].

With the entry of virus through the ACE-2 receptors into the endothelium, the major unfolding of events are as follows: activation of neutrophils and macrophages, setting off of complement cascades and production of thrombin. These events cause formation and eventual deposition of microthrombi in the cerebral vasculature, as evidenced by autopsy findings of hypoxic and ischemic injuries and infarcts in the brain. The complement cascades have also been implicated to promote microglia-induced synaptic pruning, suggesting genesis of psychosis as one of the neuropsychiatric symptoms of COVID-19 [4,5]. The effects of SARS-CoV-2 on the brain are irrefutable and comprise a decisive part of the symptomatology spectrum of COVID-19. An important area of concern is the long-term neuropsychiatric sequelae which significantly contributes to the disease burden, posing to be a major public health concern [6]. The ultimate development of curative interventional techniques necessitates a clear understanding of the underlying pathologies; hence, warranting a comprehensive neurological and psychiatric evaluation. Urgent and combined efforts need to be set forth to further elucidate the cellular and molecular mechanisms of the viral infection of the brain.

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