Rare Neurological Effects Associated with COVID-19

Abdul Rafay Shahzad

1st Year MBBS, Islamabad Medical and Dental College, Islamabad Pakistan

Key Points
➢ Origin of covid-19. ➢ Entry of SARS-COV-2 into the central nervous system. ➢ SARS-COV-2 neurotropism. ➢ Presence of SARS-COV-2 in astrocytes and neurons. ➢ Damage to olfactory epithelium by SARS-COV-2. ➢ SARS-COV -2's capability of altering genes expression. ➢ SARS-COV -2's association with Parkinson's disease. ➢ SARS-COV -2's association with encephalopathy.

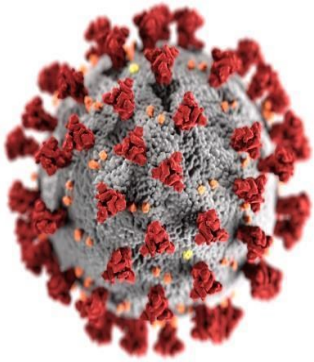

Figure: *SARS-COV-2*

SARS-CoV-2, a highly deadly coronavirus, was discovered in Wuhan (China) in December 2019. The COVID-19 pandemic was triggered by a novel virus that causes severe pneumonia and is rapidly spreading over the world. SARS-emergency CoV-2's had, and continues to have, terrible socioeconomic consequences. The impact of COVID-19 on vulnerable populations must be assessed in order for governments to alter their actions. Increasing scientific data suggests that persons should be monitored following an acute SARS-CoV-2 infection; indeed, some clinical signs persist even after recovery. There is consensus on the importance of determining which symptoms persist after infection and which disability may develop as a result of COVID-19. Various organs may be damaged, according to recent studies, case reports, and novel contributions, and neurological symptoms are present in around one-third of COVID-19 patients. Delirium, brain inflammation, stroke, and nerve damage are among possible neurological consequences after a severe COVID-19 infection.[1]

Neurological effects of SARS-COV-2

Angiotensin 2 (ACE2) and neurophilin-1 pathways in the olfactory epithelium have been heavily investigated in acute COVID-19 as a direct entrance of the virus to the CNS. This is corroborated by the findings of Bryche et al. (2020), who found that olfactory epithelium damage is linked to Sars-Cov-2 infection. A hematogenous pathway has also been suggested. Several postmortem studies on COVID-19 victims indicated indications of Sars-CoV-2 neurotropism, with viral RNA discovered in several brain regions including the olfactory system, brainstem, cerebellum, and frontal lobes. Sars-CoV-2 was also found in astrocytes, in addition to neurons. It's worth noting that the dynamics and replication of Sars-CoV-2 may differ depending on the brain cells. Both neurons and astrocytes were infected in the Crunfli et al. (2021) investigation, however astrocytes made up the great bulk of infected cells. The astrocytes' viability was shown to be diminished. Based on these findings and the different roles of neurons and, it may be worthwhile to investigate whether and how clinical representations of COVID-19 related symptoms differ between patients who

have widespread Sars-CoV-2 infection in neurons and those who have Sars-CoV-2 infection primarily in astrocytes. So yet, the specific methods of interaction between Sars-CoV-2 and brain host cells, as well as their catastrophic implications, are unknown. Sars-CoV-2's presence in frontal lobes has been linked to down-regulation of hypoxiarelated genes and up-regulation of hemoglobin genes, suggesting that it is capable of altering gene expression.[2]

Although SARS-CoV-2 has been confirmed to colonize the CNS, the implications on neurons at a molecular level are only theorized. However, it's worth noting that the virus may impact brain areas implicated in the early stages of Parkinson's disease neurodegeneration. Many COVID-19 patients did experience anosmia and ageusia, which are two hallmark PD prodromal symptoms. SARS-CoV2 could infiltrate the brain via the olfactory pathways and spread to the piriform and infra-limbic cortex, the basal ganglia, and the brainstem. According to neuropathological evidence, Lewy body aggregation in PD begins in the olfactory pathway and subsequently spreads to other brain areas via olfactory system connections, resulting in neuronal degeneration. This potential overlap between the spread of SARS-CoV2 and the spread of PD neuropathology is especially concerning when we consider that some COVID-19 patients do not recover (or only partially recover) their smell sense, indicating a possible neuronal injury that could trigger the synucleinopathy cascade. SARS-CoV-2 may enhance the risk of PD by inducing a systemic inflammatory state, in addition to the direct invasion of the CNS. In the immune response to viruses, cytokine production is critical. Excessive and dysregulated release of interferons (IFNs), interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and chemokines (C–C motif chemokine ligand, CCL-2, CCL-3, and CCL-5), which shape the so-called cytokine storm, can be harmful, inducing immune-mediated attacks on human organs. The considerable increase in C-reactive protein (CRP), IL-6, IL-8, IL-10, IL-2R, and ferritin blood levels in COVID-19 patients indicates a systemic inflammatory state. Patients with Parkinson's disease have a similar profile of peripheral inflammation, with greater blood levels of CRP and pro-inflammatory cytokines (IL-6, TNF, IL-1, and IL-2), which are strongly connected with clinical severity. As substantial experimental data reveals, COVID-19-induced inflammatory activation may affect systemic homeostasis at the CNS level, where it may activate and feed early stages of synucleinopathy, favoring the onset of Parkinson's disease.[3]

A third of COVID-19-infected critically ill patients develop encephalopathy, generally with frontal lobe-related symptoms, at the outset of illness or during hospitalization, and encephalopathy is linked to higher mortality and poor functional outcomes. Although encephalopathy has been documented in COVID-19 patients of all ages, individuals over the age of 60 and those with pre-existing neurologic disorders (stroke, dementia, Parkinson's disease) are the most impacted, especially when severe respiratory infection is present. While encephalopathy in the aforementioned circumstances is most likely multifactorial, studies of patients with encephalopathy in the absence of severe respiratory illness point to additional potential pathways, such as bio-energetic failure and vascular dysfunction in SARS-CoV-2 infection. Similar to sepsis-associated encephalopathy, a link between encephalopathy and morbidity exists regardless of respiratory illness. Encephalopathy is caused by mitochondrial malfunction, excitotoxicity, and macro- or micro-ischemic damage in non-COVID-19 individuals. In a sample of 67 hospitalized, deceased COVID-19 patients, a recent post-mortem investigation in New York found brain micro-thrombi. Confusion and cognitive dysfunction might emerge from small subcortical ischemic episodes. Due to compromised cerebral endothelial cells, patients may experience multifocal cerebral micro-hemorrhages or vascular leakage. Non-specific white matter hyper-intensities, diffusion limitation, micro-hemorrhage, and leptomeningeal enhancement are all radiographic findings in COVID-associated encephalopathy. A study of COVID-19 and encephalopathy patients in the intensive care unit (ICU) found bilateral

frontotemporal hypo-perfusion in all patients who received perfusion imaging for altered mental status. Surprisingly, up to 46% of patients with COVID-19 and concomitant encephalopathy had normal brain MRI. On fluorodeoxyglucose (FDG)-PET scans, patients with COVID-19 and cognitive impairment revealed reduced metabolism in the fronto-parietal areas.[4]

References

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