SARS-CoV-2 getting into the brain: neurological phenotype of COVID-19, and management by nano-biotechnology

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Human coronavirus infection getting into the brain: By February 2022, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, causing the coronavirus disease 2019 (COVID-19) outbreak, has infected around 415 million people, and caused ~5.8 million deaths worldwide (WHO, https://covid19.who.int/). As SARS-CoV-2 replicates during the infection, it undergoes genetic mutation to generate variants with varying characteristics and tropisms. The broad distribution of SARS-CoV-2 infection, including hyposmia, headache, dizziness, ataxia, cerebrovascular injury, hypogeusia, nausea, encephalitis, encephalopathy, vomiting, delirium, psychosis, ischemic stroke, neurocognitive syndrome, acute respiratory distress syndrome, and affective disorders. These symptoms are significant in one-third of the COVID-19 infected population causing severe diseases in both acute (less prominent) and chronic (dominating) phases, as the possibilities of SARS-CoV-2 getting into the brain have been demonstrated. However, the long-term effects of COVID-19, especially neurologic complications, are only beginning to be evaluated, and robust data are lacking. In the present situation, the significance of COVID-19 infection-related neurological complications created new NeuroCovid associated challenges as specific diagnostic, management, and therapeutic strategies are needed to be implemented (Cárdenas et al., 2021). Thus, the plausibility that SARS-CoV-2 can neuroinvasive the central nervous system (CNS) and how it affects brain cell functions has raised the demand of detail studies. The careful and critical analysis of COVID-19 patients confirmed SARS-CoV-2 RNA and proteins presence in their cerebral spinal fluid and brain. Although viral loads were relatively low, neurological sequelae in longer-time scenarios have been suggested (Cárdenas et al., 2021; Krasemann et al., 2021). The SARS-CoV-2 exhibits typical tropism, including neurotropism, as demonstrated recently. In general, spike protein (SP) of SARS-CoV-2 interacts with host angiotensin-converting enzyme 2 (ACE2) receptor, and the receptor binding domain to facilitate virus entry and initiate the viral replication process. Additionally, virus entry is also facilitated by other proteins such as integrins, neuropilin-1, and the transmembrane proteases serine 2 and serine 4 (TMPRSS2 and Tmprss4, respectively) (Krasemann et al., 2022; Mostafavi et al., 2022). The broad distribution within the CNS of ACE2 receptors, which is the main receptor for SARS-CoV-2 entry, raises concern, as ACE2 receptors are found in various cell types in the brain, including neurons, microglia, astrocytes, and endothelial cells. As of now, several SARS-CoV-2 variants have been identified that can affect the brain, including Delta (B.1.617.2), Omicron (B.1.1.529), and Alpha (B.1.1.7) variants. These variants can affect the CNS by different mechanisms, including the enhancement of viral replication in the brain, leading to neuroinvasion, neuroinflammation, and neurodegeneration. Furthermore, neuroinvasive variants of SARS-CoV-2 can affect the CNS through direct viral infection of brain cells or indirectly by inducing inflammation and immune response.

COVID-19 infection is affecting the CNS system: Besides receptor-mediated entry of SARS-CoV-2 into the CNS, its tropism towards endothelial cells of the CNS triggers the BBB disruption, which also allows the infiltration of virus-carrying leukocytes and monocytes to multiple regions of the brain. In the CNS, SARS-CoV-2 infects neurons, astrocytes, oligodendrocytes, and glial cells through ACE2 and TMPRSS2, triggering a neuroinflammatory response with astroglial and microglial activation (McQuaid et al., 2021; Pacheco-Herrero et al., 2021). Simultaneously, systemic infection leads to an overactive and dysregulated immune response. In the situation of COVID-19 infection, the level of plasma inflammatory mediators, including interleukins, chemokines, cytokines, and antibodies is increased, triggering apoptosis of epithelial cells, and leading to vascular leakage, also contributing to the increased BBB permeability. The neuroinflammatory response is known to affect brain function via altering neurotransmitter release, activating cell lysis, inducing apoptosis, and disrupting neuronal transcriptional pathways contributing to neurotoxicity, neuroinflammation, and neurodegeneration. Moreover, recent research has demonstrated that the immune response along with oxidative stress in infection with SARS-CoV-2 replication may increase the beta-amyloid neurotoxicity, a widely believed pathological hallmark of neurodegeneration in Alzheimer’s disease (Chircosta et al., 2021). The involvement of SARS-CoV-2 infection in proteopathic seed spreading via facilitating intercellular cargo transfer has been demonstrated (Liu et al., 2021) for exploring the process of α-synuclein aggregation (Semerdzhiev et al., 2022) and increasing the hyperphosphorylation of tau protein (Raman et al., 2020), promoting neuronal degeneration in Parkinson’s disease and Huntington’s disease, respectively.

Indeed, patients who suffer from acute respiratory symptoms are found at potentially high risks for long-term residual neuropsychiatric and neurocognitive disorders, including depression, obsessive-compulsive disorder, psychosis, Parkinson’s disease, and Alzheimer’s disease (Figure 1B). Considering expected pathophysiological changes, clinical neurological indicators of NeuroCovid are explained as 1) starting from the damage in epithelial cells of the nose and mouth with related hyposmia and anosmia, through the occurrence of blood clots in the brain and immune-mediated damages cranial and peripheral nerves with symptoms of fatigue, hemiplegia, aphasia, and ataxia seizures, encephalopathy, and 3) death due to the strokes and damages (Fotuhi et al., 2020).

Nanobiotechnology to manage brain function during and post COVID-19 infection: Large-scale and frequent testing is a key step to track COVID-19 infection, precaution, and sensitization to control SARS-CoV-2 transmission and combinational therapeutic approaches have emerged as the best way to manage severe and lethal forms of COVID-19 outbreak, including its neurological phenotype. As of now, molecular polymerase chain reaction-based and nucleic acid amplification (10 viral RNA copies) is still a standard analytical tool to perform selective COVID-19 diagnostics. However, nucleic acid-based diagnostics are time-consuming and require well-equipped laboratories, which requires sophisticated laboratories and skilled personnel, limiting COVID-19 diagnostics under-provision and under-performance as our reliance on tests with long turnaround times causes delays in patient receiving the required treatment. Developing sensitive and selective biosensors for rapid detection of SARS-CoV-2 at a low scale in crude human fluids at point-of-care (POC) testing has been recommended as the best alternative to manage infection. Advancements in functional nanostructures enable the development of sensitive chips and microfluidic systems for developing POC and improving SARS-CoV-2 testing. The SARS-CoV-2 infection can be monitored using a monoclonal antibody specific to SP to develop SARS-CoV-2 SP fentomole level (Ahmadivand et al., 2021). For example, a miniaturized plasmonic immunosensor using nanostructured gold nanoshell coated with a monoclonal antibody specific to SP is developed for the detection of SARS-CoV-2 SP fentomole level (Ahmadivand et al., 2021). These POC systems can be integrated with IoMT (Internet of Medical Things) technology with POC to explore telemedicine and IoMT-assisted POC testing can shorten time to treatment decision-making as well as reduce clinical crowding and virus transmission as a result of neuroCOVID-19 management requires a careful short-term and long-term neurological symptoms analysis for their prevention. Moreover, IoMT-based COVID-19 diagnostics at POC can spot subtle signs and detect mental illnesses with high accuracy and precision (Figure 1C. Jain et al., 2021; Mostafavi et al., 2022).

Due to emerging new SARS-CoV-2 variant of concern, COVID-19 is still a threat to mankind as the new variants have different but serious health consequences. This situation raises the demand to re-evaluate the performance of established COVID-19 management strategies, mainly treatment approaches based on these nanomaterials have been useful to trap (virus-like particles) and eradicate SARS-CoV-2 (nanomedicine approach for targeted drug delivery) and certainly will be capable of preventing the virus (Figure 1D). In this direction, nanomedicines will certainly be developed to protect against premature
degradation of antigens, increased cell membrane, including the BBB, permeability, sustained release, improved drug stability, on-demand controlled drug release, and enhanced immunogeneity; therefore, they can act as carriers and adjuvants. Achieving therapeutic concentrations in target tissues and adjuvant strategies to improve efficacy are significant for lowering the dosing of vaccines and vaccines, and thereby widening their therapeutic and safety window (Tiwari et al., 2021). Based on patient medical profiling and current biomonitoring, artificial intelligence-supported nano-biotechnology can be more applied for personalized prevention and treatment, contributing to a population-based cure (Figure 1C). Additionally, the formulation of pharmacologically relevant therapeutic cargos designed using multiple drugs is in demand not only to eradicate SARS-CoV-2 but also for repairing affected or damaged neurons along with other CNS cells (Tiwari et al., 2021, 2022; Mostafavi et al., 2022). Ongoing efforts also involve development strategies modulating SARS-CoV-2 immunity. Vaccines capable of generating mass immunization still stand priority for controlling the pandemic. Their efficacy related to long-term prevention and stopping transmission in broad populations requires tackling challenges associated with variability within and across individuals, including geographic and age-related differences as well as the evolutionary trajectory of SARS-CoV-2 (Machhi et al., 2021).

Taken together, during the COVID-19 pandemic, SARS-CoV-2 infection-related neurological phenotypes were increasing continuously and declared as a serious concern. Such neuroCOVID-19 caused in pre-/post-COVID-19 infection implies the appearance of both short-term and long-term neurological sequelae, including neurodegenerative disorders. Management of this neurological phenotype of COVID-19 requires applying appropriate approaches, especially addressing the BBB-associated challenges, both in diagnostics and treatment as well as controlling the pandemic through herd immunity development. High-performance nano-systems offer sophisticated protection, detection, and treatment of SARS-CoV-2 infection, including neurological phenotypes, both at individual and population scales, which seem to be a promising strategy for managing COVID-19 in a personalized manner (Figure 1D).

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