ACS Chemical Neuroscience

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Viewpoint

Neurological Insights of COVID-19 Pandemic

Gaurav Das, Nabanita Mukherjee, and Surajit Ghosh*

Cite This: *ACS Chem. Neurosci.* 2020, 11, 1206–1209

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ABSTRACT: The novel coronavirus SARS-CoV-2, which was identified after a recent outbreak in Wuhan, China, in December 2019, has kept the whole world in tenterhooks due to its severe life-threatening nature of the infection. The virus is unlike its previous counterparts, SARS-CoV and MERS-CoV, or anything the world has encountered before both in terms of virulence and severity of the infection. If scientific reports relevant to the SARS-CoV-2 virus are noted, it can be seen that the virus owes much of its killer properties to its unique structure that has a stronger binding affinity with the human angiotensin-converting enzyme 2 (hACE2) protein, which the viruses utilize as an entry point to gain accesses to its hosts. Recent reports suggest that it is not just the lung that the virus may be targeting; the human brain may soon emerge as the new abode of the virus. Already instances of patients with COVID-19 have been reported with mild (anosmia and ageusia) to severe (encephalopathy) neurological manifestations, and if that is so, then it gives us more reasons to be frightened of this killer virus. Keeping in mind that the situation does not worsen from here, immediate awareness and more thorough research regarding the neuroinvasive nature of the virus is the immediate need of the hour. Scientists globally also need to up their game to design more specific therapeutic strategies with the available information to counteract the pandemic. In this Viewpoint, we provide a brief outline of the currently known neurological manifestations of COVID-19 and discuss some probable ways to design therapeutic strategies to overcome the present global crisis.

KEYWORDS: *COVID-19, hACE2, SARS-CoV-2, encephalopathy, neuroinvasive property, therapeutic intervention*

COVID-19 is currently a global pandemic impacting around 212 countries and has already claimed the lives of more than 79,385 individuals worldwide with confirmed cases globally now standing at around 1,356,780.[1] Experts across the world warn that the disease, which originated in the Wuhan district of China in the December of 2019, will only propagate more and the present numbers are likely to inflate further. The sudden outbreak of COVID-19 shook the scientific fraternity, and scientists across the world are working tirelessly to understand the virus and its properties in order to design intervention strategies to combat the disease. So far, we have been able to understand that COVID-19 is caused by a virus known as SARS-CoV-2, which is a single-stranded RNA virus (ssRNA) with a genome size of 29903 bp. SARS-CoV-2 belongs to the same beta-coronavirus clade of the previously reported SARS-CoV and MERS-CoV and bears sequence similarity to SARS-CoV.[2] In fact, not only do they bear similarity in sequences, but also the entry point of both the viruses in humans is through the same receptor recognition. The virus SARS-CoV-2 has been speculated to have been transmitted from bats to human considering the fact that evidence of a similar coronavirus, RaTG13, has been reported in bats.[3] SARS-CoV-2 is made up of three structural proteins, namely, the spike (S), envelope (E), and membrane (M), which makes up the viral envelope, and the nucleocapsid containing the RNA genome. It is the spike protein that carries out the frontline action for the virus by performing the initial receptor recognition with the human angiotensin-converting enzyme-2 receptor (hACE2).[3] It is this interaction of hACE2 with the viral spike protein that is central to the viral infection.

ENTRY ROUTE AND CONCOMITANT PATHOPHYSIOLOGY OF COVID-19

The crystal structure of SARS-CoV-2 has revealed the presence of a core and receptor-binding domain (RBD) that is more specifically involved in recognizing the hACE2. Though both SARS-CoV and SARS-CoV-2 exploit the same receptor hACE2 in humans to gain entry into the host, the SARS-CoV-2 binding is more compact with a four residue motif from 482 to 485 in the hACE2 ridge, thus enhancing the binding affinity of SARS-CoV-2 over SARS-CoV for hACE.[3] Moreover, the two viral hot spots, namely, hot spot-31 and hot spot-353 on hACE2, are stabilized more by the SARS-CoV-2 RBD as compared to SARS-CoV.[3] All this clearly indicates why SARS-CoV-2 has a selective advantage over SARS-CoV in causing infection and is a more evolved and lethal strain.

The major clinical manifestation of SARS-CoV-2 is severe pneumonia causing immense respiratory distress in the patients, specially the aged or those with already pre-existing conditions. SARS-CoV-2 leads to chronic inflammation of the lungs, severe dyspnea, fever, dry cough, and cyanosis and in more vulnerable patients a complete lung failure.[4] ACE2, which is the entry point for SARS-COV-2, has almost a

Received: April 9, 2020
Accepted: April 10, 2020
Published: April 22, 2020

https://dx.doi.org/10.1021/acschemneuro.0c00201
ACS Chem. Neurosci. 2020, 11, 1206–1209

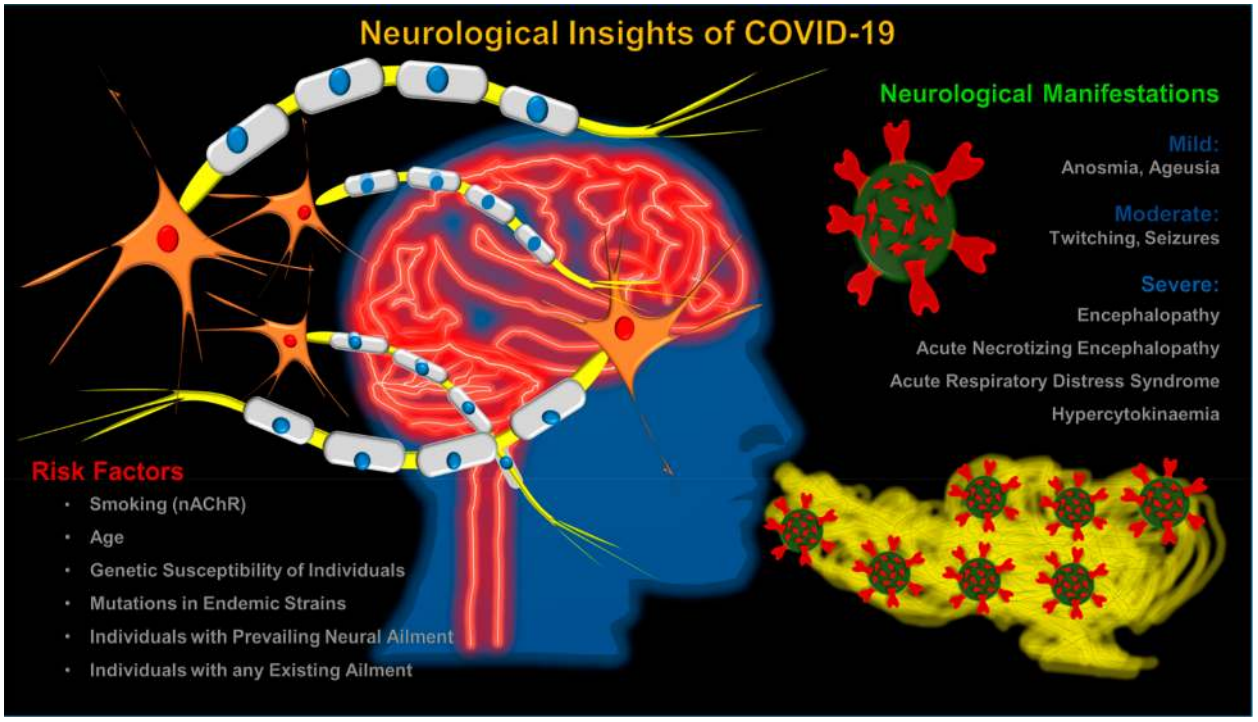

Figure 1. Cartoon with schematic representation shows an overview of neurological insights due to COVID-19 infection.

ubiquitous presence in human organs including lung parenchyma, gastrointestinal tract, nasal mucosa, renal and urinary tract, human airway epithelia, lymphoid tissues, reproductive organs, vascular endothelium, and brain.[4] The virus is believed to enter chiefly through the nasal mucosa or the gastrointestinal tract due to their higher expression of protein hACE2. The intriguing part though is that recently reported studies have noted altered mental health in some COVID-19 patients showing symptoms like anosmia and ageusia thereby indicating a neuroinvasive nature of the virus.[2]

■ ENCEPHALOPATHY AND THE CYTOKINE STORM IN COVID-19

The neurological manifestations of SARS-CoV-2 have been recently recognized from CT scan images and MRI scan of the brain of a patient who contracted COVID-19 and showed symptoms of necrotizing hemorrhagic encephalopathy.[5] Acute necrotizing encephalopathy (ANE) is a rare disorder leading to brain dysfunction mostly caused by viruses, which results in seizures, liver problems, and mental disorientation following infection.[5] The disease is characterized by multifocal symmetric lesions in the brain, which affect the brain stem, thalami, cerebellum, and cerebral white matter. ANE causes neuroinflammation resulting from a cytokine storm characterized mainly by the production of the interleukin-6 (IL-6), secreted by the macrophages, which in turn have been activated by the granulocyte−macrophage colony-stimulating factor (GM-CSF) produced by the helper T cells.[6,7] The resultant cytokine storm may also cause a surge in interleukin (IL)-2, IL-7, interferon-γ, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α leading to hyperinflammation.[6] This systemic inflammation causes severe encephalopathy in the patient, and that may lead even to stroke. Specifically, in this patient infected with SARS-CoV-2 showing ANE, the MRI images displayed clear evidence of hemorrhage through hypointense signal intensity in the susceptibility-weighted images and increase in the rim on the postcontrast images.[5]

■ SMOKERS ARE LIVING ON THE EDGE

The likeliness of COVID-19 patients to contract neurological infections can be exacerbated by secondary factors like smoking, which according to a pilot study can enhance the chances of contracting COVID-19 based neuroinfections due to the functional interactions between hACE2 and the nicotinic receptor (nAChR).[8] The same study reports that due to the coexpression of hACE2 and nicotinic acetylcholine receptor (nAChR) in many cells, there exists a functional link between them. So, when smokers smoke, it augments the expression of the hACE2 due to the nicotine stimulation of nAChR.[8] Hence, while performing autopsies on brains of COVID-19 patients, it would be wise to conduct smoker versus nonsmoker based analysis as this will help to shed light on smoking being an additional risk factor in COVID-19 patients along with age and already existing ailments.[8]

■ CNS INVASION AND SYMPTOMS

Now, as encephalopathy has been identified as one of the symptoms of COVID, the neuroinvasiveness of SARS-CoV-2 needs to be assessed to fully understand the neurological implications of COVID-19. The brain reportedly, like most other organs, expresses the hACE2 considered to be the entry point of the SARS-CoV-2 viruses in humans and is therefore not immune to viral infection. Though SARS-CoV-2 is yet to be detected in cerebrospinal fluid, SARS-CoV with similar structural and functional features has been detected in the cerebrospinal fluid of patients, indicating the ability of the virus to breach the extremely rigid blood−brain barrier.[4] If previous studies with other CoVs are taken into consideration, SARS-CoV-2 like its other family members will first infect the

https://dx.doi.org/10.1021/acschemneuro.0c00201
ACS Chem. Neurosci. 2020, 11, 1206−1209

peripheral nerve terminals and then slowly crawl its way through the synapse-connected route into the CNS.[7] Previous studies in the relevant field with SARS-CoV and MERS-CoV observed that they infiltrate the brains of transgenic mice when administered intranasally.[4] The infiltration of the virus into the brain took place through the olfactory nerves, eventually affecting the thalamus and the brain stem. The brain stem was eventually observed to be the worst infected.[4] So, following these experimental studies along with the hematologic spread of SARS-CoV-2 in CNS, retrograde neuronal transport of the virus through the vagal nerve afferents from the lungs into the CNS must be taken into consideration.[7] Also, with reports claiming infection of the gastrointestinal tract by SARS-CoV-2, the virus could even use the enteric nervous system and its sympathetic afferent neurons to reach the CNS.[7]

Now with the reports of involuntary breathing, hyposmia, and ageusia in COVID-19 patients, scientists have started to speculate that not only does SARS-CoV-2 infects lungs but it has severe implications in neurons, specifically those in the medulla oblongata, which regulates breathing, lung, and heart functions, and any damage to it can result in chronic respiratory distress as reported in COVID-19 patients.[4] It has been put forward that the latency period of the virus may be enough to actually destroy the neurons in the medullary region of the brain and can lead to coma or death (Figure 1).[4] As reports of SARS-CoV-2 reaching the blood−brain barrier through the circulating blood and breaching it by attacking the endothelial layer to gain access to CNS emerge, the virus might just be using an alternating route in the form of the olfactory bulb instead of the common hematological route.[2] If this is to be considered, the virus might just be making its way into olfactory mucosa, mostly consisting of olfactory neurons along with blood vessels and epithelial cells. The olfactory mucosa is connected with the olfactory bulb through the cribriform plate, which is found at the very base of the frontal lobes of the brain.[2] This very much explains the hyposmia and other neurological symptoms that are being increasingly observed in COVID-19 patients (Figure 1). The point to note here is that the long-term effects of the neuroinvasive nature of the virus may result in an increased risk of neurodegenerative diseases with involvement in the pathogenesis of neurological disorders like Parkinson's disease or multiple sclerosis.[7] The conditions are more likely to be worsened in COVID-19 patients with pre-existing neurological disorders.

THE THERAPEUTIC WARRIORS AGAINST COVID-19

From the evidence accumulated in various studies and the very nature of CoVs possessing neuroinvasive properties, the neurological manifestations of COVID-19 cannot be ignored. Those patients reporting early neurological symptoms, like loss of taste or smell or even seizures, must be tested for COVID-19 and kept under constant observation of neurologists as we know the latency period may be enough for the virus to completely annihilate the medullary neurons and threaten the life of the patient.[4] Also, more autopsies of not only the lungs but brains need to be performed in order to gain deeper insights into the neurotrajectory of COVID-19 infection. In this hour of great distress, therapeutic interventions from scientists across the globe are needed in order to fight this pandemic (Figure 2). As discussed at the beginning of this Viewpoint, we have made good progress in understanding the key interactions between the hACE2 and the RBD of the spike

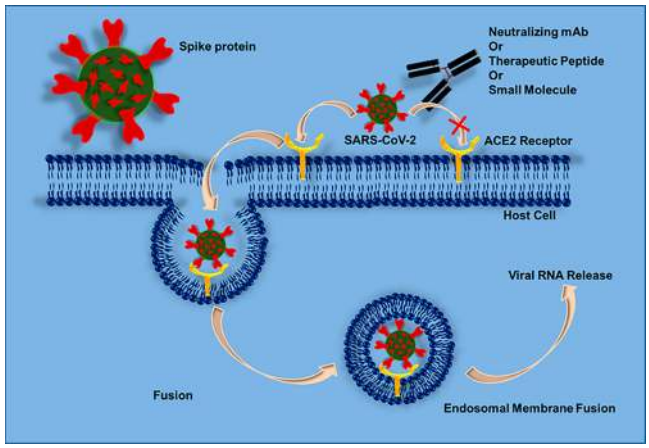

Figure 2. Cartoon with a schematic representation of the route of COVID-19 infection and potential strategy for therapeutic intervention.

protein in SARS-CoV-2.[3] Hence, we could utilize that to develop some good antiviral intervention strategies. Some antibody drugs could be designed following the epitopes on the SARS-CoV-2 RBD. Also, RBD can itself be used to test its efficacy as a subunit vaccine.[3] Since the nature of the interactions between RBD and hACE2 are protein−protein interactions, designing of peptide-based therapeutics could also be explored (Figure 2).[9] Many more such structure-guided therapeutics like small molecules or peptides that interfere with the receptor recognition of the virus could possibly halt the progression of the disease (Figure 2).[9] In fact, inhibition of transmembrane serine protease 2 (TMPRSS2), the surface protease that cleaves the viral spike protein to unleash the full infective potential of the virus, also known as the priming of the virus, was once considered to be an effective therapeutic intervention to stop the viral spread only later to be dropped owing to the unknown physiological impact of TMPRSS2 blockade.[7] Also patients with reported hyperinflammation caused by the cytokine storm should be administered appropriate steroids, selective cytokine blockers like atlizumab, antibody therapy, and inhibitors of the JAK pathway.[6]

THE GEOGRAPHICAL TOPOLOGY OF COVID-19 PANDEMIC

Another important feature, which we must consider before deploying treatment modalities to patients, is the genetic predisposition and susceptibility of the patient under consideration, which may vary at the population level across variable geographical locations. A recent study published before the massive outbreak of SARS-CoV-2 in Europe and the United States of America (USA) tried to screen for ACE2 mutants that would resist attachment of the S-protein of the virus in different populations but was not able to find any direct evidence. But thereafter, as COVID-19 slowly engulfed the entire world, a new study has indicated variations observed in the spike surface glycoprotein (Ala930Val) in the Indian SARS-CoV-2 strain as compared to the strains from the USA, Italy, Wuhan, and Nepal.[10] The same study also reported the presence of an antiviral miRNA, has-miR-27b, only unique to the Indian host population, which surprisingly even binds to the mutated region of the Indian SARS-CoV-2 strain.[10] miR-27b is known to inhibit HIV-1 replication and is widely regarded as an antiviral miRNA. The above claims of the study

https://dx.doi.org/10.1021/acschemneuro.0c00201
ACS Chem. Neurosci. 2020, 11, 1206−1209

are further corroborated by the failure of anti-HIV regimens to cure patients in China while the same anti-HIV drugs seem to have worked in some Indian patients. Along with this, it is now being widely speculated by many that widespread Bacillus Calmette−Guérin (BCG) vaccination in countries like India may have boosted the immunity of the country's thriving population and may be now serving as a protective shield against the widespread COVID-19 attack across the world. Countries without such universal policies on BCG vaccination like Italy, the U.S., or the Netherlands are among the worst hit by COVID-19 infection. Unarguably such claims require more elaborate scientific proof to be accepted as facts, but ethnicity and regional diversity do play a role in responding to such pandemics that can be affirmed without doubt. This only highlights the need for more genetic screening and population-based genome-wide studies in divergent geographical regions in order to better understand the host−pathogen interactions in a region-specific manner, which could pave the way for the genesis of more region-specific therapeutics and treatment regimens.

CONCLUSION AND VIGNETTE OF THERAPEUTIC INTERVENTION

Hence, taken together the neurological consequences of COVID-19 revealed over the last few days of the outbreak, patients reporting altered mental health or an inability to taste or smell can no longer be ignored and must be tested for COVID-19 without fail. Moreover, these patients or patients with existing neurological conditions should be monitored closely so that the symptoms do not aggravate over the subsequent days of the infection. This strategy could also be considered as a preliminary screening strategy in case of large scale community transmission of COVID-19. The prevailing health care units taking care of infected patients must now include neurologists to gain more perspective into the nature of the infections, which have a high chance of turning out to be neurological. Meanwhile, more autopsies on brains of COVID-19 patients with neurological symptoms need to be performed to establish the neuroinfection track of the disease so that appropriate measures can be taken. Along with these more engrossing therapeutic interventions ranging from passive antibody therapies to SARS-CoV-2, structure-guided molecular design needs to galvanize the entire scientific community.

AUTHOR INFORMATION

Corresponding Author

Surajit Ghosh − *Department of Bioscience & Bioengineering, Indian Institute of Technology Jodhpur, Jodhpur, Rajasthan 342037, India; Organic and Medicinal Chemistry and Structural Biology and Bioinformatics Division, CSIR-Indian Institute of Chemical Biology, Kolkata 700 032, WB, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-8203-8613; Phone: +91-291-280-1212; Email: sghosh@iitj.ac.in

Authors

Gaurav Das − *Organic and Medicinal Chemistry and Structural Biology and Bioinformatics Division, CSIR-Indian Institute of Chemical Biology, Kolkata 700 032, WB, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-8432-5384

Nabanita Mukherjee − *Department of Bioscience & Bioengineering, Indian Institute of Technology Jodhpur, Jodhpur, Rajasthan 342037, India;* orcid.org/0000-0002-0228-5148

Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00201

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

G.D. thanks ICMR and N.M. thanks MHRD and IIT Jodhpur for their fellowships. S.G. kindly acknowledges SERB India (CRG/2019/000670) for financial support and IIT Jodhpur for initiation grant and infrastructure.

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