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SARS-CoV-2, More than a Respiratory Virus: Its Potential Role in Neuropathogenesis

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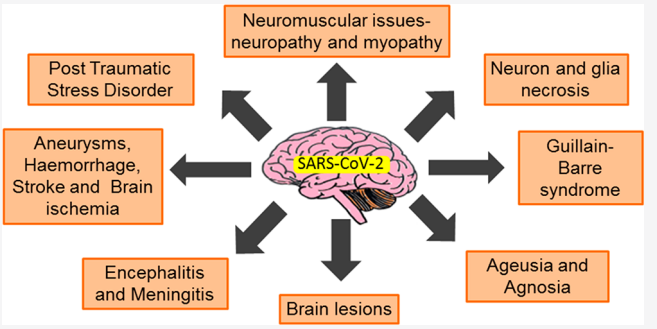
ABSTRACT: The coronavirus disease-19 (COVID-19) pandemic has emerged as one of the major outbreaks to be mentioned in history in coming times. Like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a respiratory virus infecting the lungs with fever, dry cough, and acute pneumonia being the major symptoms. It infects epithelial cells expressing angiotensin converting enzyme 2 (ACE2) receptor, which is crucial for viral entry. Based on evolving clinical evidence, it is now unfitting to label SARS-CoV-2 as just a respiratory virus, as lately there are various reports that substantiate its pathogenicity in other organs of the body, including brain. In this review, we discuss the epidemiology of SARS-CoV-2 in comparison to SARS and MERS along with possibilities of viral entry into central nervous system (CNS) tissues. The review provides detailed information about the virulence, epidemiology, and insights into molecular pathways involved in the infectivity of the SARS-CoV-2 virus, along with an in-depth view of current concepts about the neurological significance of the SARS-CoV-2 virus and its neuropathological competence. The review also touches upon our current understanding of placental transmission of SARS-CoV-2, an important aspect of vertical transmission. Furthermore, the review provides a current update on strategies that have been used, are being used, or are under trial for treating the disease.



KEYWORDS: *COVID-19, SARS, MERS, ACE2, CNS, brain, neuropathogenesis, neurodegeneration*

INTRODUCTION

A novel coronavirus infection with pneumonia-like symptoms appeared in the Hubei district of Wuhan in China toward the tail end of 2019. This disease was first reported to the World Health Organization (WHO) office on 31 December 2019.[1] Phylogenetically, its original source is speculated to be bat, but the seafood and wild animals sold in the market area could have possibly been an intermediate source leading to the transmission to humans.[2] This outbreak has impacted the entire world, so WHO later announced this to be a pandemic on 30th January 2020. The name COVID-19 was coined by WHO on 11th February 2020. Simultaneously, the International Committee on Taxonomy of Viruses (ICTV) finalized the scientific name "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" for this novel coronavirus.[3]

As per the ICTV classification, coronaviruses belong to the family of Coronaviridae, which falls in the order Nidovirales. These are further segregated into four subfamilies, Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, based on their phylogenetic and genomic data. Among these, the alpha and beta are known to infect only mammals, whereas the gamma and delta infect birds and very rarely mammals.[4] SARS-CoV-2 is a typical betacoronavirus and has similar makeup to that of Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) that caused a similar epidemic in 2002.

Being a respiratory disease virus, the most common mode of transmission is through air droplets and contact. There have been reports where the virus has been detected in the urine and feces of patients even after pharyngeal swabs tested negative, and hence feco-oral route through contaminated water or poor hygiene can also be a possible route of transmission, but this needs to be substantiated further with more carefully designed studies.[5] Flu-like symptoms, namely, fever, dry cough, and fatigue, are the most common ones, with a few cases also showing sputum discharge, headache, and diarrhea. Very recently there have also been reports of brain pathogenesis, encephalitis, and involvement of brain areas

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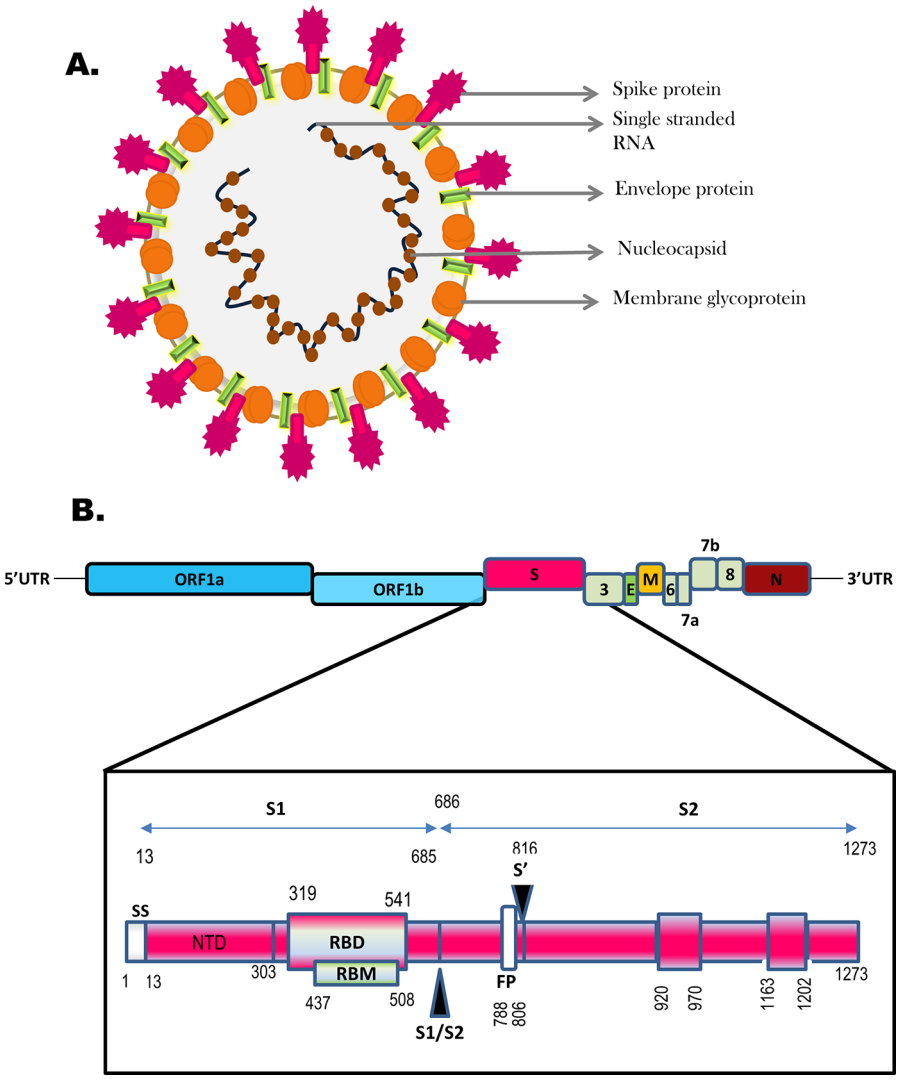

Figure 1. (A) Structure of SARS-CoV-2 virus. (B) Genomic sequence of SARS-CoV-2 showing position of the open reading frames (ORF1a and ORF1b), spike (S), envelope (E), membrane (M), and nucleocapsid (N) as arranged from 5′-UTR to 3′-UTR, along with the sequence of spike protein (1−1273 amino acids, involved in ACE2 receptor recognition and internalization of the virus) showing the receptor binding domain (RBD) and the proteases S1/S2.

important for respiratory control, which necessitated the compilation of this review.

This review focuses on the virulence, epidemiological aspects, and underlying molecular pathways for infectivity of the SARS-CoV-2 virus and potential therapies against it. We also emphasized the pathogenesis of the SARS-CoV-2 virus in the brain along with fetal transmission.

STRUCTURE AND VIROLOGY

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), like all other coronaviruses, is an enveloped virus comprising a long single-stranded positive sense RNA genome of size of 29 903 nucleotides[6] coupled to a nucleoprotein contained in a capsid. The glycoproteins protrude through the envelope toward the outside as spikes. The genome of every betacoronavirus has six open reading frames (ORFs). It is arranged from 5′ to 3′ and starts with ORF 1a and 1b coding for the replicase gene. This is followed by the structural genes, S (spike), E (envelope), M (membrane), and N (nucleocapsid), and in some coronaviruses, there is an additional HE (hemagglutinin-esterase). Receptor binding and membrane fusion for internalization of the virus is executed by the S protein. The E protein is an integral membrane protein with ion channels and membrane permeabilizing activity. E protein is known to participate in virion assembly and morphogenesis and has been characterized as a virulence factor in the case of SARS-CoV. The N protein not only plays a role in encapsulating the RNA but is also involved in the translation and synthesis of the viral genome. SARS-CoV is 79% similar to SARS-CoV-2[7−9] (Figure 1).

EPIDEMIOLOGY

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The SARS-CoV epidemic emerged in November 2002 in southern China and spread rapidly to the world until 2003. The epidemic started as atypical pneumonia in patients and transmitted to the health workers through nosocomial transmission in Foshan, China.[10,11] The traveling of infected individuals within China and around the world was the major cause of spread of the virus. A total of 8096 cases were reported with 774 deaths

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having a case fatality rate (CFR) of 9.6% in 29 countries by the end of the epidemic in July 2003.[12] The basic reproductive rate (R_0) of SARS-CoV was 2.3−3.7. A reconsideration of evolutionary history points toward the zoonotic transmission of SARS-CoV, whereas genetic analysis of SARS-CoV suggests that there is 95% sequence homology with the bat CoV.[10,13]

MERS-CoV was first reported in Jeddah, Saudi Arabia, almost a decade after the SARS-CoV outbreak. A patient died due to severe pneumonia and multiorgan failure, which was identified as the first case in 2012.[14] Social gatherings and traveling are said to be the main cause for spread of the infection to around 27 countries. As of November 2019, WHO had been notified of 2494 laboratory-confirmed cases of infection with MERS-CoV, including 858 fatalities (CFR, 34.4%).[15] R_0 of MERS-CoV was 0.50−0.92. The primary MERS-CoV origin remains unclear, though dromedary camels are identified as the host reservoir.[10]

SARS-CoV-2/COVID-19. The epidemiological phase was marked by local spread of novel coronavirus infected pneumonia (NCIP), which is epidemiologically linked with a wholesale market in Wuhan, Hubei Province of China, and emerged in December 2019. Contact transmission had occurred in the initial phase as the number of confirmed cases were rising. Later international travel by air and family transmission within the region marked the next phase that started after January 13, 2020, as the first case was reported in Thailand outside of China. The spread was so rapid that the exponential growth of the cases within mainland of China and other foreign countries appeared a mere 2 weeks after this, by January 26, 2020. The R_0 of SARS-CoV2 is estimated as 1.4−5.7. As SARS-CoV and MERS-CoV were controlled by rapid testing and social distancing and R_0 dropped, a similar approach was adopted by China and other nations facing the brunt of COVID-19 spread, which was later advised by WHO as well.[13] The three closely related viruses that affected global populations have certain similarities among them in terms of symptoms, incubation times, natural reservoirs, sex ratios, strategies for infection control, and origin of infections, as well as differences in terms of fatality rates, R_0, etc., summarized in Table 1, along with their clinical phenotypes in Table 2.

Table 1. Summary of Major CoV Diseases

	SARS-CoV[13,16,17]	MERS-CoV[13,16]	SARS-CoV-2[13,18,19]
time of epidemic	November 2002	July 2012	December 2019
place of origin	Foshan, China	Jeddah, Saudi Arabia	Wuhan, China
intermediate host	palm civets and racoon dogs	dromedary camels	bats and pangolins?
natural reservoir	Chinese horseshoe bat	bat?	bats or pangolins?
case fatality rate (CFR)	9.6% (as of July 2003)	34.4% (as of November 2019)	13.9% as of meta-analysis
incubation period (days)	4−6	2−14	1−14
strategies to limit spread	isolation and testing	social distancing	hand washing, social distancing, quarantine
basic reproductive rate (R_0)	2.3−3.7	0.50−0.92	1.4−5.7
human to human transmission	high	limited	high

Table 2. Comparative Clinical Phenotypes of Major CoV Diseases

clinical features	SARS-CoV[20,21]	MERS-CoV[22]	SARS-CoV-2[a13,23]
general	fever (>38 °C), chills, malaise, myalgia, shivering	fever (>38 °C), chills or rigors, body pain, lethargy, anorexia, myalgia, malaise	fever (>38 °C), chills, fatigue, muscular soreness
central nervous system (CNS)	headache	headache and confusion	claustrophobia, encephalitis, dysfunction in sense of smell and taste, Guillain−Barre syndrome (GBS)
respiratory tract[b]	cough (initially dry) shortness of breath, sore throat	URT: runny nose, sore throat, sneezing. LRT: cough (dry or with sputum), hemoptysis, chest pain and dyspnoea	URT: runny nose, sore throat, sneezing. LRT cough-dry, chest pain, dyspnoea, respiratory failure, fibrosis
gastrointestinal (GI) tract	diarrhea, nausea, and vomiting	appetite loss, nausea, vomiting, abdominal discomfort, diarrhea	diarrhea and vomiting, abdominal discomfort
sex ratio	more in males than females	more in males than females	more in males than females
abnormal clinical findings[c]	lymphopenia, elevated ALT, LDH, and CPK, thrombocytopenia, abnormal chest X-ray, pneumonia	abnormal chest X-ray and CT scan, lymphopenia, leukopenia, thrombocytopenia, elevated liver enzymes (LDH, ALT, AST)	viral detection by chest and throat swab, X-ray abnormalities including bilateral patchy shadows or ground glass opacity in lungs, hypoxemia, multiple organ failure, lymphopenia
complications[d]	ARDS, pneumothorax	severe acute respiratory syndrome, multiorgan failure, septic shock	ARDS, multiple organ failure
factors associated with increased mortality	old age, chronic hepatitis B, high LDH, diabetes mellitus	comorbidities, including chronic disease of lungs, kidney, liver, or heart and cancer, immunosuppressive drugs, age >65 years, presence of pleural effusion, low serum albumin	those with high blood pressure, diabetes, cancer, and older age have higher mortality rate

[a]Apart from symptomatic conditions various asymptomatic cases are reported making the diagnosis in SARS-CoV-2 patients even more challenging.[24] [b]URT, upper respiratory tract; LRT, lower respiratory tract. [c]ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRK, creatine phosphokinase; AST, aspartate aminotransferase; CT, computed tomography. [d]ARDS, acute respiratory distress syndrome.

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ANGIOTENSIN CONVERTING ENZYME 2 (ACE2) MEDIATED SARS-CoV-2 PATHOGENESIS

Very much similar to SARS-CoV, the mode of SARS-CoV-2 viral entry into the cells is via ACE-2 receptors, which are highly expressed on the lung epithelium.[25,26] Quite lately, gastrointestinal disturbance like diarrhea and vomiting has also been pointed out as one of the symptoms for SARS-CoV-2 even in the absence of respiratory issues, showing the susceptibility of intestinal epithelial cells to SARS-CoV-2. This is perhaps due to the high expression of ACE2 receptors expressed on these cells.[27,28]

Angiotensin-converting enzyme-2 is made up of two domains, an N-terminal carboxypeptidase homologous to ACE and a C-terminal domain homologous to collectrin.[29] The carboxypeptidase of ACE2 cleaves angiotensin II to Ang 1−7, thereby negatively regulating the renin−angiotensin system, eventually playing a protective role in the cardiovascular system, whereas the collectrin homologue is responsible for the internalization of the neutral amino acid transporter B(0)AT1 and absorption of amino acids in the intestine and kidneys.[30,31] Along with these two functions, ACE2 was identified as the sole functional receptor for the SARS-CoV pathogenesis.[32,33] As ACE2 plays a role as a negative regulator in lung pathogenesis by modulating the renin−angiotensin system, its downregulation *in vivo* and *in vitro* in cells infected with SARS-CoV proves its crucial role in viral infection.[34,35] Contrary to this, there are reports where endothelial cells that do not express detectable or high levels of ACE2 have also shown SARS-CoV infection, revealing that alternate receptors may facilitate other cell types to be prone to infection.[36] Viral entry into the cells is mediated by the spike (S) protein in case of SARS-CoV. The S protein comprises an amino (N)-terminal S1 subunit and a carboxy (C)-terminal S2 subunit. The S1 subunit is crucial for recognition of and attachment to the ACE2 receptor on the host cell and hence is the determining factor for cell tropism and host range of the viruses.[37] SARS-CoV spike protein interaction with ACE2 receptor reveals dissociation of S1 with ACE2 inducing S2 transition from the metastable prefusion to the more stable postfusion form that is prerequisite for membrane fusion.[38,39] In SARS-CoV, when the viral S1 subunit of the S protein binds to the ACE2 receptor, entry into the cell is facilitated by cellular proteases, with cleavage at the S1/S2 and the S2′ site which eventually permits viral entry into the cell with the help of S2 subunit. Transmembrane protease serine 2 (TMPRSS2) is the cellular serine protease involved in S protein priming. As SARS-S and SARS-2-S have 76% amino acid identity, it was later proven that the viral entry of SARS-CoV-2 is also mediated through the same pathway by engaging ACE2 and TMPRSS2 similarly to SARS-CoV.[40−42] ACE2 was found to bind to the SARS-CoV at the receptor-binding motif located in the receptor-binding domain in the spike protein. ACE2 in humans interacts with Y442, L472, N479, D480, T487, and Y491 amino acids in case of SARS-CoV, whereas SARS-CoV-2 spike protein interacts with L455, F486, Q493, S494, N501, and Y505. Even though the interacting amino acids are different, the general ACE2 receptor-binding motif interface remains similar.[43,44] In silico analysis also showed the high affinity of the SARS-CoV-2 spike protein toward ACE2.[45]

Apart from lungs and intestine, various other organs express ACE2 like heart, kidney, spleen, and brain.[46] Therefore, other organs positive for ACE2 expression may likely be susceptible to SARS-CoV-2 infection. In the brain, neurons and glial cells are known to express ACE2, and previously SARS-CoV has been detected in the brain of infected patients.[47] Owing to these studies on the pathogenesis of SARS-CoV and the corresponding ongoing research on novel SARS-CoV-2, the main viral entry portal of SARS-CoV-2 still remains via ACE2 receptor binding (Figure 2) and is currently the only known

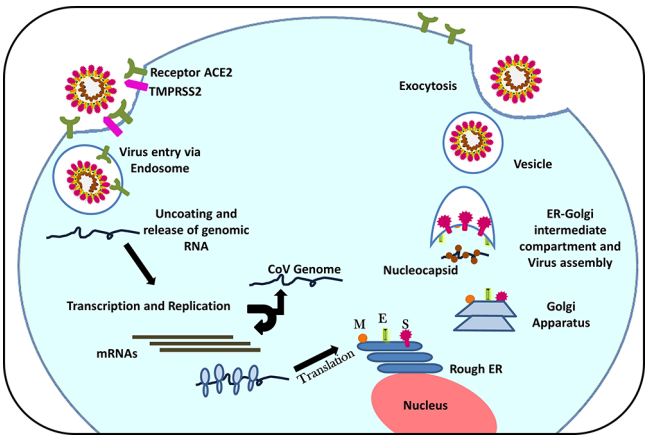

Figure 2. Replication cycle of SARS-CoV-2 in host cell. The receptor binding domain (RBD) of the virus interacts with ACE2 receptor and TMPRSS2 on the host cell, which is responsible for protease action and aids the viral entry by endocytosis. The viral genome uses the host polymerase machinery to transcribe and translate the viral genes. These are processed through the rough ER and Golgi apparatus and then the viral proteins are assembled, thereby releasing the virus from the infected cell by exocytosis.

receptor even in brain pathogenesis. But as mentioned earlier, certain ACE2 negative cell types showed positive infection; therefore it would be crucial to investigate if there are other interacting proteins assisting in its entry into the cells. This can be ascertained with gene manipulation studies and assay of any alteration in SARS-CoV-2 susceptibility of a particular cell type.

NEUROPATHOLOGY OF SARS-CoV-2

As the majority patients show fever, dry cough, breathing difficulties, and fatigue as symptoms, SARS-CoV-2 was primarily characterized as a respiratory virus affecting mainly the lung alveolar cells. Many viruses, like human immunodeficiency virus (HIV), Japanese encephalitis virus (JEV), and Zika, possess the ability to infect the central and peripheral nervous systems and are identified to be neurotrophic in nature. Speculations of SARS-CoV-2 infections in the central nervous system can be drawn from past respiratory disease epidemics like SARS-CoV and MERS coronavirus, where various reports demonstrated the presence of virus in brain. SARS-CoV viral load was found in brain neurons, along with its presence in epithelial cells, lung tissues, thyroid and parathyroid glands, adrenal cortical cells, monocytes in lymph nodes and spleen, etc., as revealed by autopsy reports.[48,49] A group of scientists from Taiwan showed that patients with SARS had severe neuromuscular issues like neuropathy and myopathy, substantiating the evidence for its neurological aspect.[50] This further supported the idea that coronaviruses can infect and damage nerve cells. Using an animal model, one of the seven respiratory viruses, HCoV OC43, was found to propagate through neuron−neuron transmission in cell culture

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via axonal transport.[51] Later, a few studies strongly supported the fact that SARS infects brain neurons, evidently showing that even low expression of ACE-2 in brain neurons was sufficient to cause infection in the brain and that the virus traffics to the brain through the olfactory nerve and causes transneuronal spread leading to the death of the animal. This death was attributed to either dysfunction or death of infected neurons.[52,53] The presence of virus was also shown in SARS brain tissue using electron microscopy. Upon exploring the brain tissue pathology, there was necrosis of neuronal cells, and gliocytes were marked with hyperplasia along with CD68+ monocytes and macrophages and CD3+ T lymphocytes infiltrating the brain mesenchyme supporting brain inflammation due to viral infection.[54] These studies further helped in strengthening the role of coronaviruses in neurological symptoms in SARS patients.

A case study report from Riyadh revealed that MERS positive patients exhibited severe neurologic syndrome comprising alteration in consciousness even leading to coma, ataxia, and focal motor deficit. MRI of these patients showed bilateral hyperintense lesions residing in the white matter and subcortical areas of the frontal, temporal, and parietal lobes, the basal ganglia, and the corpus callosum.[55] MERS virus like SARS has shown infection in the brain, perhaps because DPP4, the receptor for MERS virus binding, is also expressed in the brain cells of humans and other mammals.[56] Transgenic mice with human DPP4 developed lethal disease with encephalitis. This data only showed that astrocytes and neurons are susceptible to infection because of the presence of the binding receptor DPP4, but viral entry into the brain was not explored in detail. There is also a lack of postmortem data to support the presence of viral particles in the brain cells, which may be explored in the future from archival tissues. So if the MERS virus were to enter the brain, it has sufficient DPP4 receptors to support and spread infection in the brain, suggesting the likely hood of possible infection and subsequent neurological deficits in MERS survivors as a sequelae.[57] Not just SARS and MERS, but various the respiratory viruses like influenza A (H5N1), and HEV coronavirus have shown potential to be neurotrophic and infect brain cells. They have been shown to gain entry into the brain through afferent nerves of vagal, trigeminal, and olfactory origin, once they have replicated in respiratory mucosa, or through trans-synaptic transmission via endo- or exocytosis.[58−62] All these previous instances of viral infection outbreaks and their effects on the central nervous system provide insights into the possibility that SARS-CoV-2 may cause brain pathogenesis.

One of the critical steps for SARS-CoV infections that later impacts adsorption, host compatibility, tissue tropism, and eventually its pathogenesis stems from spike protein cleavage by host proteases.[63] It was recently reported that the spike protein of SARS-CoV-2 possesses a furin-like cleavage site that is specific and is not present in other betacoronaviruses, although there are close similarities in the genetic makeup of various betacoronaviruses, as well as SARS-CoV.[64] An association between the furin-like cleavage sites and its proteases in host have been demonstrated to be critical for the determination of neurotropisms in viruses of the Coronaviridae family,[65] and hence the presence of the unique furin-like cleavage sites in SARS-CoV-2 may help the virus to be neurotropic and enable it to infect CNS tissues. This also suggests that furin inhibitors directed toward the unique furin cleavage sites of SARS-CoV-2 offer an attractive opportunity that must be explored by drug discovery groups.

Loss of taste (ageusia) or smell (agnosia) has been observed as one of the symptoms in many upper respiratory diseases, and COVID-19 disturbing the olfactory system is certainly conceivable. In various case reports of COVID-19 patients, loss of smell and taste have been predicted as early signs of infection even in certain cases where the patients showed no nasal symptoms.[66−68] The loss of olfaction is mainly found to be due to damage to the olfactory epithelium, which expresses ACE-2 receptors for viral entry and infection. In many COVID-19 cases, loss of smell and taste is temporary and recovered post-treatment, so it is hypothesized that the damage is only at the epithelial level as olfactory neurons once damaged will not be regenerated and it would take longer time.[69] There has been no evidence that it damages the olfactory neurons. But as mentioned earlier, there have been reports of SARS entry into the brain via the olfactory bulb, and another study hints toward the possible role of the cribriform plate near the olfactory bulb and epithelium. Therefore, further investigations into this area are warranted to further strengthen the SARS-CoV-2−brain connection.[52,67] MRI imaging of patients with postinfectious olfactory loss showed a decrease in the volume of the olfactory bulb.[70] So study of COVID-19 patients with anosmia can reveal additional data about olfactory disruption. Hence it is reasonable to suggest that although SARS-CoV-2 virus may or may not be affecting the olfactory bulb, but it surely may be a critical route for viral entry into the brain (Figure 3).

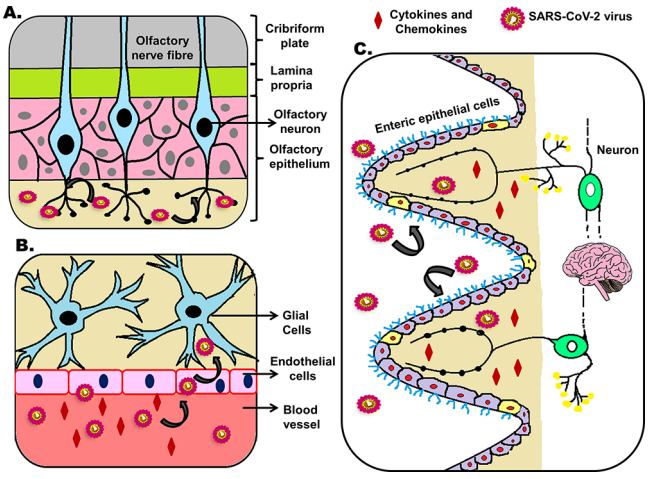

Figure 3. Possible routes of entry of SARS-CoV-2 virus in the brain. (A) The most probable entry route for the SARS-CoV-2 is through the infected olfactory epithelium passing through the cribriform plate via olfactory nerve fibers into the brain. (B) Through compromising the endothelial cell lining of the blood−brain barrier (BBB) caused mainly by cytokine storm in the blood. (C) Through the brain−gut axis by infecting the enteric nervous system caused by damage to the enteric epithelial cells due to inflammatory cytokines and chemokines.

As mentioned before, the virus has been detected in the stool of COVID-19 patients, and the brain−gut axis is highly linked. The intestinal epithelium also expresses ACE2 and TMPRSS2 receptors and is a potential target for SARS-CoV-2 infection.[71,72] In fact SARS-CoV-2 is detected in the entire gastrointestinal (GI) tract of COVID-19 patients.[73] Although it is still not clear, the virus, similar to the case of olfactory epithelium, can infect and damage intestinal epithelial cells,

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eventually gaining entry into the CNS through the nerve endings innervating the intestinal wall like the vagal nerve (Figure 3). Anorexia, vomiting, and nausea are common symptoms in COVID-19 patients, which can occur due to infection of either the GI tract or the lateral hypothalamic nuclei, which correlates with the gut−brain axis.[74] This observation offers exciting new avenues for research and focused efforts to establish the brain−gut connection in COVID19 patients and to investigate the entry mechanism of SARS-CoV-2 at molecular and cellular levels.

In a study conducted on COVID-19 patients in Wuhan, 36.4% of patients showed neurological symptoms like headache, unconsciousness, and skeletal muscle injury, although these symptoms were mainly observed in acute infections rather than mild infections.[75] The first ever case of meningitis reported due to SARS-CoV-2 infection was found in a 24-year old man with no international travel history. Initial symptoms seen were headache, generalized fatigue, and fever. The patient showed neck stiffness along with transient seizures lasting for a minute. The SARS-CoV-2 RNA was detected in the cerebrospinal fluid (CSF) of the patient but surprisingly not in the nasopharyngeal swab. The brain MRI scans revealed hyperintensity along the wall of the right lateral ventricle accompanied with hyperintense signal changes in the right mesial temporal lobe and hippocampus. Another case from Los Angeles was a 41-year old female showing meningoencephalitis without any respiratory complications. The collective reports from this patient vividly open up the fact that meningitis and encephalitis are possible in SARS-CoV-2 infection even if respiratory symptoms are not exhibited.[76,77] Acute necrotizing encephalopathy (ANE), which is mostly found in children and has been previously linked with influenza and other viral diseases, was detected using CT scan and MRI in an adult infected with SARS-CoV-2.[78] The possibility of SARS-CoV-2 infection in the brain is substantiated due to the presence of ACE2 receptors on neurons and glial cells. The SARS-CoV-2 virus may damage the blood−brain barrier (BBB) endothelial lining by binding to ACE2 receptors and traffic into the brain (Figure 3). Elevated level of cytokines and chemokines is the inflammatory response in the immune system in all kinds of viral infections. SARS-CoV-2 infection also has shown an increase in cytokines like monocyte chemoattractant protein 1 (MCP-1), interferon γ-induced protein 10 (IP-10), interleukin (IL)-4, IL-10, IL-1B, and interferon γ (IFN-γ) even in mild infections and also tumor necrosis factor-α (TNF-α), MCP-1, and granulocyte colony stimulating factor (GCSF) in severely ill patients.[79] This cytokine storm as the immune response can compromise the BBB increasing the influx of leukocytes into the brain leading to seizures and encephalitis.[80] After it gains entry into the brain, it can bind to the ACE2 receptors on neurons and glia to facilitate neuronal damage and inflammatory response.[81] The binding of the SARS-CoV-2 viral particles to ACE2 may cause high blood pressure leading to a high risk of cerebral hemorrhage.[82] One case of SARS-CoV-2, an aneurysmal subarachnoid hemorrhage was detected with systemic inflammation, although it is not yet clear whether the hemorrhage was due to SARS-CoV-2 infection. As viral infections are known to cause cytokine rush leading to high systemic inflammation, this can progress to cause aneurysms.[83] ACE2 expression in the brain has previously been linked to stroke and brain ischemia. In a transgenic stroke mouse model, an increased expression of ACE2 on neurons decreased the stroke volume in the mice.[84] ACE2 is important in maintaining the balance between Ang II and Ang 1−7 by increasing Ang 1−7, eventually causing a reduction in the reactive oxygen species,[85] and overexpression of ACE2 in neurons has been shown to decrease the risk of ischemia.[84] Four patients with acute stroke were identified as being SARS-CoV-2 positive as detected by imaging and PCR.[86] So it can be speculated that SARS-CoV-2 infection in brain cells may lead to reduced expression of ACE2 and possible stroke and ischemia. A recent report showed that contrary to the presence of SARS-CoV-2 in the CSF of patients, two patients did not test positive for viral RNA in the CSF but exhibited Hunt and Hess grade 3 subarachnoid hemorrhage from a ruptured aneurysm and ischemic stroke along with flu-like symptoms suggesting that the viral load in CSF depends on the systemic viral load and neurotropism of the virus.[87] The other major basis of stroke is thrombosis, diagnosed in many COVID-19 patients. Venous and arterial thromboembolism is seen in COVID-19 patients along with elevation in D-dimer levels.[88,89] SARS-CoV-2 infection activates pro-inflammatory cytokines leading to increase in the levels of thrombin and coagulation activation along with decrease in the anticoagulants in the blood. This culminates in platelet activation and thrombosis and may be the cause behind acute ischemic stroke.[90] Hence, measuring the levels of D-dimers is crucial in possible stroke cases. Anticoagulant therapy may be helpful in the treatment of thrombotic related cases and strokes.[91]

A recent report suggested brain and spine demyelinating lesions in a COVID-19 positive patient.[92] This might cause serious distress leading to impaired motor and cognitive functions. SARS-CoV-2 may have short- or long-lasting effects on cognition and memory, as ACE-2 deficient mice are known to have poor cognition and memory.[93,94] To have a conclusive report on SARS-Cov-2 causing long-term cognitive decline, it is suggested that cognitive studies and monitoring should be pursued over the long-term on recovered patients. A case study revealed the first case of Guillain−Barre syndrome (GBS) in China in a 61-year old woman.[95] Following this case, five patients in Italy showed similar association of GBS with SARS-CoV-2. Patients showed lower limb weakness and paresthesias, facial diplegia, ataxia, and flaccid tetraplegia.[96] Further epidemiological data and in-depth studies are necessary to conclude the link between SARS-CoV-2 and Guillain−Barre syndrome.

Apart from the plausible viral infection of SARS-CoV-2 in the brain, patients cured of the disease may undergo severe post-traumatic stress disorder (PTSD), a psychological impact that is as important as systemic infection. Previous reports of SARS and MERS have clearly demonstrated the psychological impacts on the people that survived the epidemic.[97] A screening of patients that recovered from SARS indicated decline in cognitive functions along with depression, auditory and visual hallucinations, suicidal tendencies, etc.;[98] 40% of the SARS survivors that participated in the study were tracked for 4 years and clinically exhibited high psychiatric morbidities along with chronic fatigue.[99] From the MERS epidemic, many patients under quarantine along with other health care workers and professionals experienced stress, depression, fear, and anxiety due to isolation.[100] The Spanish influenza virus pandemic has been linked to schizophrenia.[101] As of now, there are no studies as to how the COVID-19 pandemic will affect the people psychologically, but on the basis of past reports of epidemics, severe emotional problems may impact the immune strength and eventually the recovery of these

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patients. Social distancing is the utmost measure to prevent spread of viral infections but is the major cause that may lead to various issues like stress, fear, depression, and anxiety. The other plausible reason for psychotic issues in patients treated for SARS-CoV-2 related illness may be the steroid drugs used for treatment, which are known to aggravate psychosis.[102] Psychological issues for all people, infected and not infected, in pandemic hit areas cannot be ignored and can have long lasting psychological scars. Thus, such issues should be of utmost importance not only during but also after the pandemic. Therefore, setting up centers for mental health and counselling is crucial to help people recover from this trauma psychologically.[103]

Many these reports support the idea that SARS-CoV-2 is causing neurological disturbances and disorders in infected patients, and therefore its consequences on the brain cannot be sidelined and are as important as the respiratory problems.[104] As our understanding of the pathophysiology of this novel coronavirus improves, it will enable us to design therapeutic strategies and reduce the devastation caused to the economy and health of populations around the globe.

■ INTRAUTERINE TRANSMISSION OF SARS-CoV-2

A few viruses have the potential to cross the placental barriers and infect the fetus. Zika virus infects the fetus through the mother by intrauterine transmission and leads to microcephaly in the fetus. Upon looking into the history of SARS and MERS, many case studies have revealed nothing related to intrauterine transmission.[105,106] As of now, there have been no reports on intrauterine transmission of the virus in COVID-19 positive pregnant women.[107,108] But there have been positive signs of the SARS-CoV-2 virus in other body fluids, and therefore the possibility of transmission during vaginal or caesarean birth cannot be negated. Also, chances of transmission to infants through cord blood transmission during birth and breast milk feeding postbirth may be taken into consideration to avoid any possibility. So, even though there are no reports of intrauterine transmission, early infant infections point more toward vertical peripartum or neonatal transmission.[109] Expression of ACE2 in maternal−fetal interface was observed mainly in the stromal cells and perivascular cells of decidua along with the cytotrophoblast and syncytiotrophoblast in placenta, which raises a plausible concern of vertical transmission from mother to the fetus or placental dysfunction or abortion in pregnant women with SARS-CoV-2 infection.[110] It is too soon to draw conclusions about the possible outcomes, and further case studies and research are quintessential in this area. A study to investigate SARS-CoV-2 infection in pregnancy and its transmission to fetuses and newborns is being funded by the National Institutes of Health, USA. It would be crucial to track the newborns not only until the infection subsides but at least until they are 14 years old to determine any neuropathological, neurocognitive, and neuropsychiatric issues that these children may develop later in their lives.[111]

■ POTENTIAL THERAPEUTICS

SARS-CoV-2 is highly contagious, and in the most severe cases, oxygen support, broad-spectrum antibiotics, antivirals, and therapies for multiple organ failure and immunomodulation are needed. The lack of drug treatment for CoVs associated with high morbidity and mortality worldwide urges a need for novel drug discovery to reduce the infectivity of the virus. Currently, there is no approved drug or therapy, either for prevention or for cure of SARS-CoV-2. Hence therapies are necessary to block the initial systemic infection that would progress to brain infections of the virus. As the cognizance of possible SARS-CoV-2 induced neuropathogenesis itself is very recent, there are actually no therapeutic agents for treating SARS-CoV-2 neuropathogenesis. Fortunately, efforts are in progress relying on either repurposing of known antivirals or development of some novel antiviral agents that can cross the blood−brain barrier.

Coronaviruses encompass a wide variety of species diversity but share key homology that can be a target for drug design purposes. SARS-CoV and MERS-CoV use the spike glycoprotein (S) as an entry pass with the receptor binding domain present on S protein interacting with ACE2 receptor and dipeptidyl peptidase 4 of the host cell, respectively.[112] SARS-CoV-2 mode of entry is also reported via ACE2 in the host cell as it shares similarity with SARS-CoV and MERS. Therefore, the S protein and the receptor ACE2 could be main immunogenic antigens,[42] and ACE2 inhibitors and angiotensin receptor blockers could be tentative therapeutics to treat COVID-19.[113,114] The endosomal or cell surface non-endosomal pathways are used by CoVs for host cell entry.[115] Chlorpromazine (CPZ), the prototype of phenothiazine-type antipsychotic drugs, having antiviral properties against several viruses like influenza,[116] Japanese encephalitis virus,[117] Zika virus,[118] hepatitis viruses,[119] and JC virus,[120] promptly crosses the blood−brain barrier and could be a likely candidate to prevent the neuropathogenesis of SARS-CoV-2.[121,122] Anti-protozoal drugs like ivermectin can inhibit nuclear transport *in vitro* in SARS-CoV, and nitazoxanide impairs intracellular trafficking in influenza virus by ERp57 protein inhibition, and they have also been used against SARS-CoV and MERS-CoV infection; hence this could also be potentially effective against SARS-CoV-2.[123−126] Some host proteases help in the activation of S protein by cleaving it into subunits, which aids the virus attachment on the plasma membrane of host cells. After cleavage, the receptor-binding domain (RBD) aids the fusion of virus to the host receptor. Some of these proteases are cysteine protease cathepsins, transmembrane protease serine 2 (TMPRSS2), and airway trypsin-like protease (TMPRSS11D) in SARS-CoV and furin in MERS-CoV.[127] Umifenovir (Arbidol) and camostat mesilate like drugs can restrict the virus entry by targeting the S protein of the virus and TMPRSS protease, respectively.[128,129] Thus these cell entry pathways can provide a way toward the drug targets either by monotherapy or by use of a cocktail of treatments with inhibitors of the host proteases, which should be further assessed. Antimalarial drugs such as chloroquine and hydroxychloroquine can stop viral entry and endocytosis by multiple mechanisms and were hence extensively used against SARS-CoV-2; unfortunately these medications are also marked with increased frequency of ventricular arrhythmia and hence should be used with great caution.[130−132] The replication machinery of the CoVs can be interrupted by some specific drugs like remdesivir, sofosbuvir, and favipiravir that can target the viral RNA dependent RNA polymerases (RdRp) and thus halt the replication and transcription of CoVs.[133−135] Ribavirin (nasal to brain administration) could be a potential treatment for neuronal COVID-19,[136] but it can also act as a teratogen so the use of this drug should be avoided in pregnancy.[137] Programmed CRISPR proteins such as Cas13[138] and silencing RNAs (siRNAs) could be an antiviral platform that can target

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the ssRNA viruses. Plasma therapy using isolated antibody from recovered patients of COVID-19 could also be used as a therapy.[139] On the other hand, cell based therapies like mesenchymal stem cells, which earlier were used as an immunomodulator in secondary progressive multiple sclerosis,[140−142] and cardiosphere-derived cells (CAP-1002) can help the patients by boosting their immunity and tissue repair mechanisms.[143] SARS-CoV-2 preventive vaccines like mRNA1273 and BNT162 are in clinical trial phases along with other RNA based vaccines showing promising results. Vector based vaccines having antigenic parts are also under assessment.[144,145] Some inactivated vaccine candidates for SARS-CoV2 tested in primates could be promising candidates for use in humans in future.[146] Also these types of systemic immune boosters may activate glial cells to safeguard the brain. There are three general approaches that can be used: first using existing drugs and immunomodulators to treat other infections; second screening of available compounds that have antiviral activity; third novel drug discovery. The novel drug discovery is a costly process and will take too much time. Therefore, in this urgent need for a treatment approach, the first two are suitable, and eventually repurposing existing drugs for other diseases like influenza, HIV, HCV, HBV, SARS-CoV, MERS, and Ebola will accelerate the process of drug development.[147]

Hyperinflammation is associated with SARS-CoV-2, and neuroimmune status might be affected due to this virus. Immunomodulators like fingolimod, which is generally used in the treatment of multiple sclerosis,[148] and recombinant cytokines and interferons like tocilizumab and sarilumab might tackle the neurological form of COVID-19.[130,149] Memantine and other adamantanes like amantadine are known to be utilized in treating Alzheimer's disease, Parkinson's disease, and influenza and are potential drugs possessing antiviral properties as well. Therefore, they can be potential drugs in preventing viral replication and treatment of COVID-19 related neuropathology.[150] Various drugs and vaccines are being tested against SARS-CoV-2 with some trials favoring the risk/benefit ratio and some not. These ongoing therapies and interventions are not standardized and need controlled clinical and research trials with future updates that are necessary during this global pandemic.

CONCLUSION

SARS-CoV-2 virus has a very high infection rate, and worldwide more than 5.1 million and 0.33 million confirmed infections and deaths, respectively, have been reported[151] with the numbers still increasing at an alarming rate. Various countries have adopted lockdown strategies to minimize social contacts, as it is the only way to prevent transmission until there is a potent vaccine against the virus. The biggest challenge of this virus is its asymptomatic presence in the population, which makes it more arduous to diagnose in the large population. Being a respiratory virus by nature, it has shown its ability to disrupt many other physiological functions, including the central nervous system. Therefore, it has now become critical to look into the widespread effects of the SARS-CoV-2 reported in the brain and its evident potency to impair CNS functions. Additionally, it is important to thoroughly investigate the entry route of the virus in the brain. There have been cases demonstrating the presence of the virus in the brain and CSF of a few patients without its presence in nasal swabs, and hence more epidemiological and autopsy data is needed to completely understand the virus. Hence autopsies must be conducted, especially in patients where some neurological signs are reported. Also, many patients who have recovered from the disease with no presence of viral load in the peripheral system should be screened for viral particles in the CSF. It is highly likely that the virus that has entered the brain may not be completely cleared due to the less efficient drug delivery caused by restrictions of the BBB. So, it is not just crucial to screen patients for brain abnormalities during treatment but also post-treatment for a couple of years. Along with systemic infection, it is of utmost importance to follow patients for psychological and cognitive impairments and to devise strategies to combat psychological trauma and stress post-treatment. Also, the ability of the virus to infect fetus through placental damage and infiltration is a high possibility and should be investigated. All infants born to COVID-19 positive mothers should be screened for conclusive results and followed later in their lives for any neurocognitive deficits. Recently some infants have also been reported to be COVID-19 positive and were later cleared of the disease. Such pediatric cases should be followed for any neurocognitive deficits until age of 14. As the spread of infections is possible by asymptomatic carriers to new hosts, widespread testing both by serological and RT-PCR tests of most of, if not entire, population would be ideal. Few treatment strategies have been successful in combating the virus, such as antiretroviral therapy, antimalarial drugs, etc., but these treatments often have major side effects in the liver, cardiovascular problems, etc. Given the situation, the only way to prevent the infection is by adopting physical distancing, covering the nose and mouth, and frequent washing and sanitizing of hands and inanimate objects of transmission, as the major hope and the only possible long time solution to eradicate the disease lie with advent of an efficient vaccine against the virus, and several promising candidates are under clinical trials.

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