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Involvement of the nervous system in COVID-19: The bell should toll in the brain

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ABSTRACT

The world is fuming at SARS-CoV-2 for being the culprit for causing the devastating COVID-19, claiming millions of lives across the globe in the form of respiratory disorders. But lesser known are its effects on the CNS that are slowly surfacing in the worldwide population. Our review illustrates findings that claim SARS-CoV-2's arrival onto the ACE2 receptors of neuronal and glial cells mainly via CSF, olfactory nerve, trigeminal nerve, neuronal dissemination, and hematogenous pathways. The role of SARS-CoV-2 structural proteins in its smooth viral infectivity of the host cannot be ignored, especially the spike proteins that mediate spike attachment and host membrane fusion. Worth mentioning the nucleocapsid, envelope, and membrane proteins make the proliferation of SARS-CoV-2 much simpler than expected in spreading infection. This has led to catastrophic conditions like seizures, Guillain-Barré syndrome, viral encephalitis, meningoencephalitis, acute cerebrovascular disease, and respiratory failures. Placing a magnifying lens on the lesser-explored CNS consequences of COVID-19, we attempt to shift the focus of our readers onto the new supporting threats to which further studies are needed.

1. Introduction

The journey of a virus causing respiratory illness that began in December 2019 has now brought us in the middle of a pandemic claiming the lives of nearly one million as of September 2020. In the beginning, having infected a lot of countries, it has now granted its mercy on a few while other countries are still in the battle with the virus. The virus termed officially by World Health Organization (WHO) as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on January 11, 2020, is known to cause COVID-19 (Coronavirus Disease-19), a disease responsible for respiratory disorders across the world [1,2]. Usually, these respiratory disorders could include breathlessness, pneumonia, and ultimately acute respiratory distress syndrome (ARDS) defined by pulmonary edema, hypoxemia, and reduction in the size of the aerated lungs [3,4].

SARS-CoV-2 contains a positive-sense single strand of RNA virus of 29,903 base pairs which belongs to the genus *Betacoronavirus* in the *Coronaviridae* family [5]. About ten open reading frames (ORF) are present in their genome. ORF1a/b translates for polyprotein 1a, polyprotein 1b, and 16 non-structural proteins (NSPs) [6]. The remaining genome codes for structural proteins and accessory proteins [7]. The structural proteins present in SARS-CoV-2 include Spike proteins, Nucleocapsid proteins, Membrane proteins, and Envelope proteins i.e. S, N, M, and E protein respectively [8]. The S protein promotes viral attachment and membrane fusion, N protein in replication of the virus in the host organism, E protein in forming viroporins essential for viral assembly and release, and M protein in virus assembly and budding [9,10].

The SARS-CoV-2 S protein binds to angiotensin-converting enzyme 2 (ACE2) receptors. Transmembrane protease serine type 2 (TMPRSS2) mediated priming of S protein subunits S1 and S2 cause activation of ACE2 receptors that enhance the attachment of SARS-CoV-2 virions and its membrane fusion with target cells [11,12]. In the initial stages of infection, it is primarily known to affect the respiratory system where the infected patients showed symptoms ranging from breathlessness to ARDS[13].

Interestingly, current reports say that SARS-CoV-2 virions have managed to evade into the brain as well, one reason could be due to the distribution of ACE2 receptors in the brain. ACE2 and TMPRSS2 are found in high proportions in precursor cells of oligodendrocytes and astrocytes residing in substantia nigra and cortex and also in the endothelial cells of cerebral capillaries and this cerebral vascular network helps SARS-CoV-2 to gain access in the central nervous system (CNS) [14]. It is also speculated that it may enter the CNS via olfactory or neuron mediated dissemination, creating a scope for evaluating other possible routes in the CNS [15]. A recent study highlights various

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neurological manifestations in patients like encephalopathy, encephalitis, Guillain-Barré syndrome (GBS), anosmia, acute cerebrovascular disease, etc. that have resulted as a consequence of COVID-19 [16].

Hence, it is now evident that SARS-CoV-2 could infect the CNS and lead to its numerous complications. Therefore, it is vital to understand the pieces of evidence for the entry of SARS-CoV-2, possible routes through which SARS-CoV-2 may enter into the CNS, potential interaction of structural proteins, and the neurological conditions that may follow and thus, our review attempts to chalk out the same.

2. Evidence for entry of SARS-CoV-2 into the CNS

2.1. Cerebrospinal fluid

The cerebrospinal fluid (CSF), in the brain is produced in the walls of the ventricles by a network of blood capillaries called choroid plexuses. Eighty percent of proteins in the CSF are derived from peripheral blood, and the cells of the CNS synthesize and release the rest of the CSF proteome. Hence, any cellular and biochemical changes of the brain may perhaps leave a mark in the CSF. Therefore, analyzing if SARS-CoV-2 exists in the CSF may explain the ability of neuroinvasion of SARS-CoV-2. The CSF of a COVID-19 patient with encephalitis showed the presence of SARS-CoV-2. Of note, hyperintensity along the right ventricle wall and abnormal findings in the hippocampus were observed [17]. In a case report, a patient showed neurological symptoms of demyelinating disease and upon subjecting to a real-time polymerase chain reaction (RT-PCR), the CSF sample was found positive for SARS-CoV-2 [18]. Recently, Cebrian and colleagues identified SARS-CoV-2 located in the patient's CSF who presented symptoms like headache and impaired consciousness [19]. In a retrospective study to evaluate the neuroimaging outcomes in extreme COVID-19 patients, the RNA of SARS-CoV-2 was identified in the CSF [20].

SARS-CoV-2 antibodies develop rapidly after infection (Fig. 1). Thus, an immune-mediated nervous system impairment may occur after a viral infection. Supporting this, the CSF of two patients having COVID-19 encephalopathy showed SARS-CoV-2 antibodies. Through enzyme-linked immunosorbent assay (ELISA), SARS-CoV-2 S and N protein antigens were detected [21]. The SARS-CoV-2 S proteins have a short intracellular C fragment, transmembrane moiety, and ectodomain element. In the ectodomain, the S1 component facilitates the receptor binding and S2 facilitates membrane fusion by stimulating adhesion to the cells and enhancing the spreading of the virus to the non-infected cells [8]. These antibodies may stimulate the glial cells leading to neuroinflammation. Neuroinflammation may lead to the production of cytokines and oxidative stress [22,23].

In COVID-19 infected patients that show neurologic symptoms, the presence of SARS-CoV-2 in CSF provided the proof for the invasion of the virus into the CNS. However, retrospective screening of 578 CSF samples in COVID-19 patients showed negative results for SARS-CoV-2. The study was performed in the general population, and the authors concluded that in such cases, the testing of SARS-CoV-2 in the CSF is not essential [24]. Furthermore, in COVID-19 induced meningitis, encephalitis, and Guillain-Barré syndrome, the SARS-CoV-2's existence in CSF was not detected [25–27]. Whether these neurologic symptoms are expressed in a specific group of COVID-19 infected patients requires exploration and added documentation in large cohorts of patients. An increasing number of research teams have screened SARS-CoV-2 in cerebrospinal fluid, with discrepant findings. Since the analysis of CSF has been carried out with different methods across different laboratories, the test quality criteria, reliability and reproducibility differ [18–20]. The technical problems of lumbar puncture is a significant drawback in the collection of CSF biomarkers. Further, the differential diagnosis between neurological disorders presenting with COVID-19 also poses a diagnostic challenge. In COVID-19 patients, neurological symptoms may arise several days after the entry of SARS-CoV-2 [27]. CSF may have a low viral load as the projected incubation period is five days and taking in to account the time between infection and sample collection [25–27]. Thus, in more subjects with neurological manifestations, the CSF SARS-CoV-2 assay needs to be validated. Due to the less understanding regarding probable neurologic complications in COVID-19, there is an urgent need for CSF studies connecting definite cases and neuropathological outcomes.

2.2. Olfactory route

Anosmia and hyposmia, the lack of ability, or diminished ability to smell have been recognized as an early symptom of COVID-19. Lately, multiple studies investigated the prevalence and clinical outcomes of olfactory dysfunction in COVID-19 patients [28,29]. Given the olfactory route may provide easy access to CNS, the prospect that SARS-CoV-2 could access the CNS through this route cannot be denied. With a

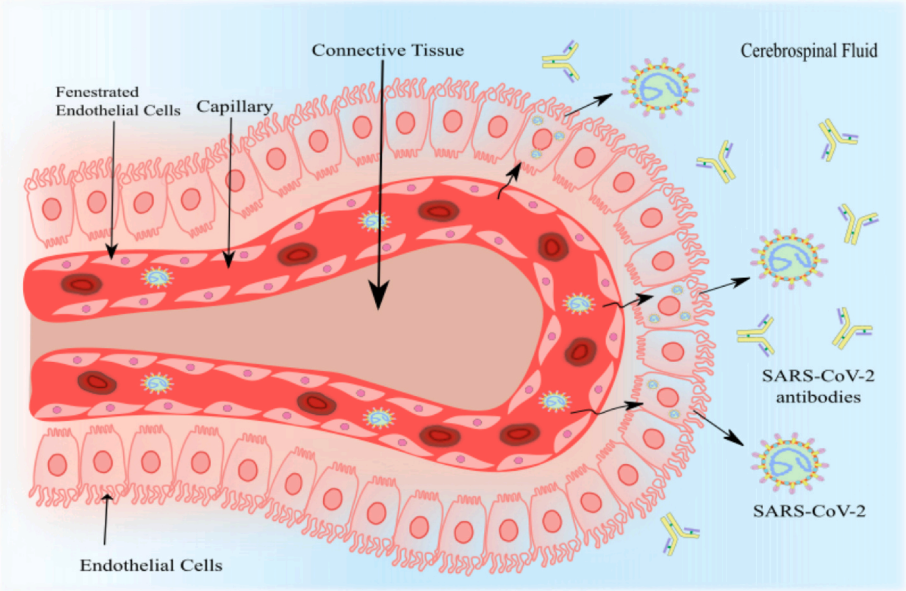

Fig. 1. The development of SARS-CoV-2 antibodies after its infection in the CSF.

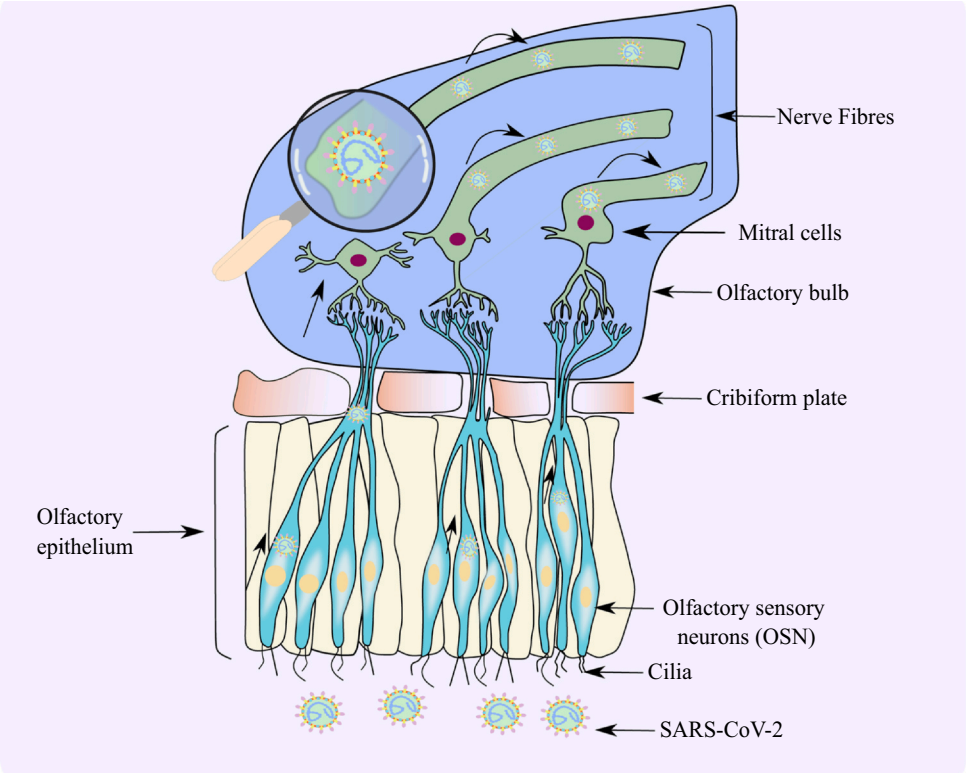

Fig. 2. The entry of SARS-CoV-2 in the CNS via the olfactory sensory neurons.

growing number of clinical studies aimed to detect the association between olfactory route and neurotropism in COVID-19 infected individuals, the concept of the neuroinvasive potential of SARS-CoV-2 has become more and more elusive.

The olfactory epithelium consists of olfactory sensory neurons (OSN) initiating the olfactory response. Cilia that project from the dendrite of olfactory sensory neurons make it accessible for the virus to infect neurons [30]. Axons of OSN extend through the cribriform plate of the ethmoid bone [31]. These bundles of axons constitute the right and left olfactory nerve which terminates in the olfactory bulbs of the brain [32] (Fig. 2). The entry of SARS-CoV-2 is dependent on the binding affinity of S protein to the ACE2 receptor followed by TMPRSS2 activity [33]. Analysis of multiple scRNA- seq datasets found a high population of ACE2 receptor and TMPRSS2 in the goblet and nasal mucosal cells lined by cilia [34]. In the golden Syrian hamster model, nasal instillation of two strains of SARS-CoV-2 (UCN1 and UCN19) caused damage in the olfactory epithelium, loss of OSN cilia, and intrusion of immune cells in the olfactory epithelium [35].

In thirty-two COVID-19 autopsy cases, the highest amount of SARS-CoV-2 was identified in the olfactory mucosa underneath the cribriform plate, olfactory bulb, trigeminal ganglion, and medulla oblongata [36]. Nevertheless, MRI evaluation showed bilateral olfactory bulb edema in an asymptomatic health worker diagnosed with SARS-CoV-2, who later experienced anosmia and dysgeusia [37]. Ultrastructural analysis of the olfactory nerve, gyrus rectus, and brain stem of COVID-19 patient revealed damage to nerve axons, glia, and myelin sheath. Further, the virions of SARS-CoV-2 were identified in these anatomic regions [38]. Supporting this, brain MRI studies in COVID-19 patients suggests injury to the olfactory bulb following the SARS-CoV-2 attack [39,40].

2.3. Trigeminal nerve

Mechanisms of neuronal complications linked with COVID-19 could be due to SARS-CoV-2 invasion of trigeminal nerve sensory axons from the mucosa of the nose. Recently, neuronal cell loss and degeneration of axon in the trigeminal nerve was observed in the autopsy of six COVID-19 patients [41]. However, whether these observations are due to an immune response or direct infiltration of the virus could not be established [41,42]. The sensory axons from three branches of the trigeminal nerve, namely ophthalmic, maxillary, and mandibular nerve enter the trigeminal ganglion and terminate in nuclei in the pons (Fig. 3). High levels of SARS-CoV-2 were found in trigeminal ganglion following an autopsy in COVID-19 infected patients [36]. Another interesting feature of the SARS-CoV-2- trigeminal nerve interaction is the connectivity of

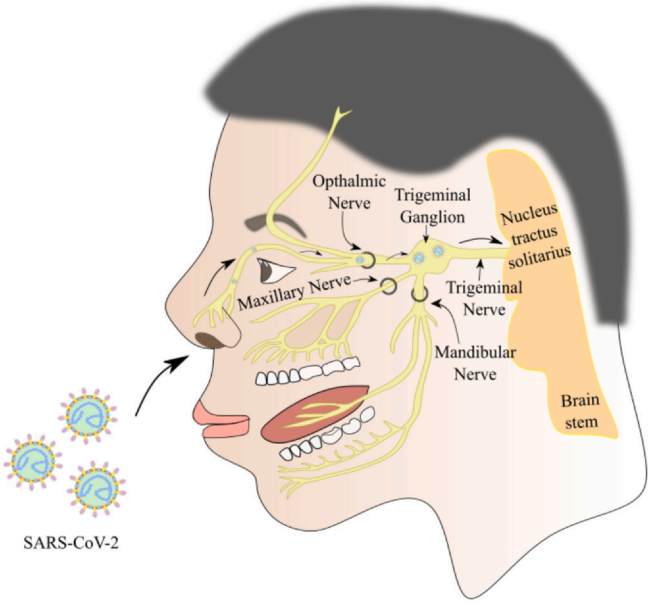

Fig. 3. Nucleus tractus solitarius infection by SARS-CoV-2 via the trigeminal nerve pathway.

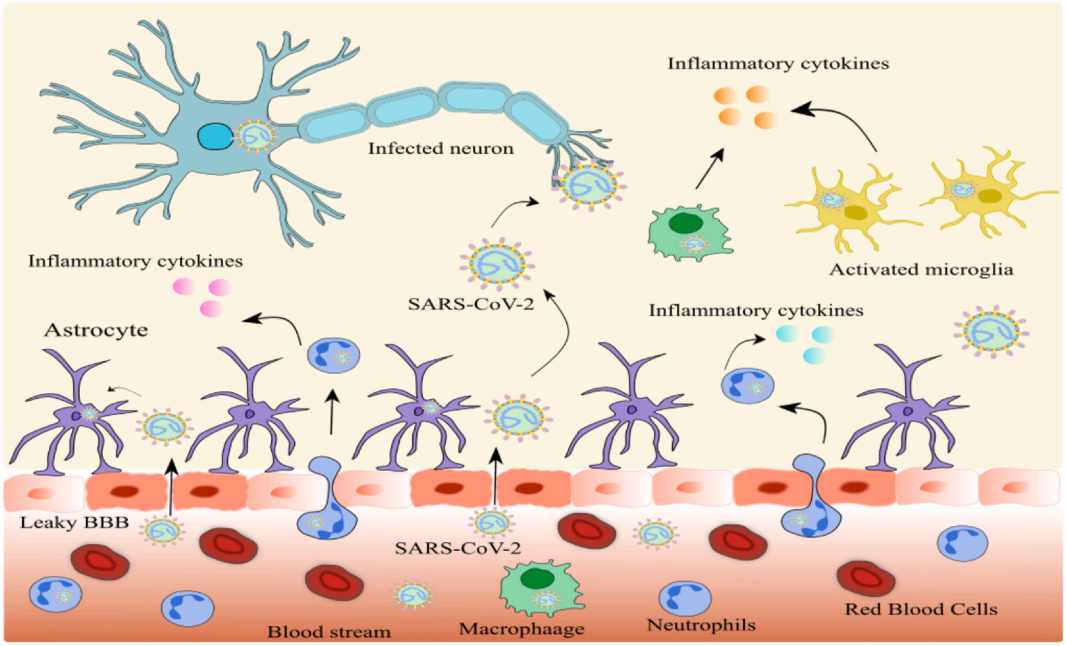

Fig. 4. The hematogenous route used by SARS-CoV-2 to infect neurons in the CNS.

the trigeminal pathway to the caudal brain regions and respiratory nuclei. This supports the notion that SARS-CoV-2 could damage the nucleus tractus solitarius (NTS) (Fig. 3) leading to microvascular clotting, pulmonary edema, and cytokine storm in COVID-19 affected patients [41].

2.4. Hematogenous route

The CNS can be affected by the respiratory viruses in case of insufficient peripheral immune clearance leading to a subsequent increase of viral load in the blood through a process termed as viremia. [32]. Via this hematogenous route, it can cause infection of blood-brain barrier (BBB) endothelial cells or epithelium of the blood-cerebrospinal fluid barrier (BCSF) in the ventricles (Fig. 1) [43]. The viruses can also gain access to the CNS via paracellular transmigration occurring due to disruptions of the tight junctions in BBB (Fig. 4) [44]. Once the SARS-CoV-2 enters the bloodstream, it can travel into the cerebral circulation leading to the interaction of S protein with ACE2 receptors in the CNS [45]. ACE2 receptors are found in the neuronal cells and glia that promote CNS invasion of SARS-CoV-2 in CNS [46]. This could be a possible reason for the increase in the levels of glial fibrillary acidic protein (GFAP) which is a biomarker for astrocytic damage and also an increase in the neurofilament light chain, a biomarker for indicating neuronal damage [47]. The patients who were infected with COVID-19 and had CNS symptoms, showed a lesser count of lymphocytes as compared to COVID-19 patients without CNS symptoms. This could be possibly due to the suppression of immunity mediated by SARS-CoV-2 [48]. Other possibilities could be the development of cytokine storm and prevention of upregulation of T cells due to their infection by SARS-CoV-2 [49].

2.5. Neuronal dissemination

Respiratory viruses also can enter the CNS through retrograde neuronal dissemination by first infecting peripheral neurons followed by axonal transport systems to access the CNS. The CNS neurons are connected to the peripheral organs, which can be used as a point of entry by the viruses that infect sensory or motor nerve endings [50]. The polarized neurons can receive and transfer data. This retrograde or anterograde transport is facilitated by proteins like dynein and kinesin [51]. An increasing number of cases have identified viral particles in peripheral nerves and the current findings elucidating the role of SARS-CoV-2 in several neurological disorders summarized in this paper, augment a converging hypothesis that axonal dissemination plays a critical role in the progression of the disease.

2.6. Gastrointestinal (GI) route

The possibility of SARS-CoV-2 infection via the GI route has also grabbed enough attention amongst the COVID-19 cases. This could be due to the abundant presence of ACE2 receptors in the glandular cells of the gastric epithelia, the duodenal epithelia, and even the rectal epithelia [52]. ACE2 receptors have also been traced in the colonic endothelial and vascular smooth muscle. Immunohistology studies have revealed the expression levels of ACE2 receptors in the small intestine [53]. With such an extensive distribution of ACE2 receptors, COVID-19 cases have bridged the connection of disease with the disruption of the digestive system expressed in terms of diarrhea, nausea and vomiting, and abdominal pain [54]. This could be a reason for the presence of SARS-CoV-2 in the fecal samples until 5 weeks after the patients testing negative for the upper respiratory swab samples [54,55]. GI tract is connected to the central nervous system through the enteric neuronal network regulated by the vagus nerve and sympathetic nerve. Certainly, the enteric invasion of SARS-CoV-2 may alter the blood and lymphatic system. Interestingly, in the report of Chen et.al, COVID-19 patients reported positive for SARS-CoV-2 RNA in fecal samples were clogged at around 67% [56]. Similarly, Xiao et.al reported approximately 54% of such cases suggesting the secretion of the viral particles from the GI cells [57], while Park et.al reported close to 4% of COVID-19 cases tested positive for SARS-CoV-2 RNA in the feces [58]. Therefore, even though such high variabilities in the reports exists, these findings are essential to project towards the prospective audience in-order to arrive at a clearer conclusion since the exact mechanism is yet to be illuminated.

3. Interaction of SARS-CoV-2 structural proteins with the nervous system

The SARS-CoV-2 that possess structural proteins namely S proteins, N proteins, E proteins, and M proteins play a crucial role in determining

the entry, incorporation, and proliferation of SARS-CoV-2 virions in the host body [8]. The structure of S protein appears like a crown due to which the virus is characteristically named as coronavirus [59]. ACE2 type receptors are widely populated in endothelia of arteries, veins, arterial smooth muscles, Type I and Type II alveolar epithelial cells, squamous epithelium of nasal and oral mucosa, and the vessels of the small intestine and colon [60]. A recent study conducted using human pluripotent stem cells (PSC) -obtained mixed neurons concluded that ACE2 is highly expressed in neuronal cell bodies and lesser in the axons and the dendrites [61]. Further, Zhang and colleagues demonstrated the ability of SARS-CoV-2 to infect the neural progenitor cells [62]. SARS-CoV-2 may gain access to CNS through routes like the olfactory nerve, trigeminal nerve, neuronal dissemination, or hematogenous route to present its neuroinvasive potential as mentioned before in Section 2. The SARS-CoV-2's S protein possesses a 10–20 fold greater binding potential with ACE2 receptors as compared to SARS-CoV (severe acute respiratory syndrome coronavirus) S protein. The receptor-binding domain (RBD) of the S1 subunit transforms to enhance virus and ACE2 receptor binding [63]. This transforms S2 to a post-fusion mode [64]. The TMPRSS II are co-expressed with ACE2 receptors and play an essential role in priming and activation of S proteins that helps in membrane fusion [65]. The sustentacular cells of the olfactory epithelium help in the sensing of odor and olfactory neuron metabolism and express a high amount of ACE2 and TMPRSS2. Therefore, SARS-CoV-2 can target these cells to ultimately reach the CNS causing olfactory system failures [66]. Similarly, SARS-CoV-2 S protein may associate with ACE2 receptors at multiple sites where it is co-expressed with TMPRSS2 to promote neuroinvasion as shown in Fig. 5.

The N protein is present in high amounts at the start of the infection and plays a role in viral replication in the host body [67]. The N protein present in SARS-CoV-2 has about 90% similarity to the SARS-CoV N proteins [68]. The peculiar feature of N protein is that it binds to the SARS-CoV RNA and packs them into a ribonucleoprotein complex [69]. The N protein contains N Terminal Domain (NTD), a Serine Rich (SR) linker region, and a C Terminal Domain (CTD). The NTD facilitates RNA binding while the SR rich linker promotes phosphorylation, and the CTD helps in oligomerization [70].

The E proteins are small proteins important in viral replication. They form small hydrophobic viroporins important in viral assembly and release. Along with these functions, they also facilitate cytotoxicity and pathogenic pathways [71]. The E proteins also play an important role in neuronal propagation, neuronal virulence, and its degeneration [72]. The E proteins also increase inflammatory responses in the host, thus enhancing the inflammation-mediated effects in hosts [73]. The M protein is the most abundant protein present in the coronaviruses [74]. It associates with the E protein to facilitate the attachment of S protein over its surface. The long-form of M proteins bends to create an enclosed membrane over the ribonucleoprotein [75]. Therefore, such synergistic functions of all the structural proteins in SARS-CoV-2 encourage its infectivity in target cells.

4. Neurological disorders associated with SARS-CoV-2

4.1. Seizures

Generally, seizures involve changes in the neurological function due to high discharge from neurons in the brain while recurrent seizures are named epilepsy. They are broadly classified into partial and generalized seizures and are characterized by loss of attention, impaired or loss of consciousness, reduced skeletal muscle contractions, etc. [76]. Patients with COVID-19 manifest seizures since the earliest stage of the disease. In a multicenter retrospective study, Lu and colleagues have evaluated the incidence and risk of seizures in 304 COVID-19 patients in China, including Hubei province, the epicenter of COVID-19 in China. The patients enrolled did not have a previous history of seizure. Seizures were observed in eighty- four cases (27%). They identified hypoxia as the most common risk factor for seizure in COVID-19 patients. However, the study suggests no indication of the risk of seizures in COVID-

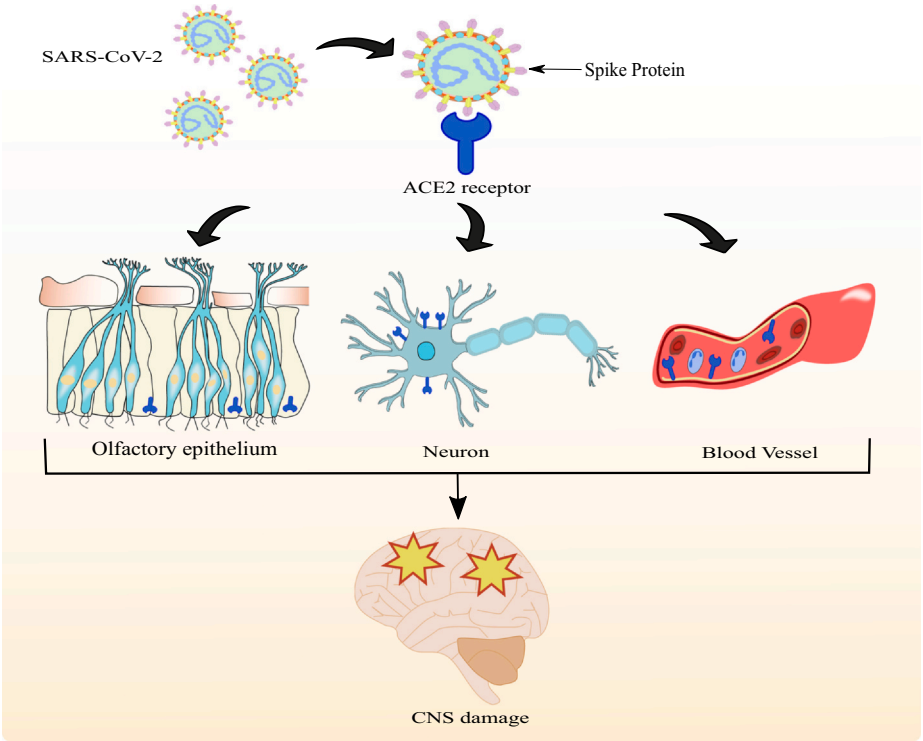

Fig. 5. Interaction of SARS-CoV-2 spike protein with ACE2 receptors at multiple sites to facilitate CNS damage.

19 affected patients [77]. On the other hand, Galanapoulou et al. in a case series of retrospective nature found that seizures were seen in COVID-19 patients and EEG investigations showed frontal sharp waves suggesting sporadic epileptic abnormalities. A frontal epileptogenic dysfunction observed may be correlated with the invasion of SARS-CoV-2 into the brain through the olfactory route [78]. A body of evidence has been formed, proposing that the COVID-19 may lead to neurologic complications [79–81]. Others have confirmed the notion that seizures could be an early manifestation of the SARS-CoV-2 attack [82,83].

Fasano et al. describe a case of focal motor seizure and Vollono and colleagues report focal status epilepticus as a presenting symptom of COVID-19. Interestingly, the body temperature of these patients was normal, and the SARS-CoV-2 infection did not show any pulmonary involvement [84,85]. In a sub febrile patient, Elgamasy and colleagues found that recurrent focal seizures could be an early manifestation of SARS-CoV-2 encroachment [86]. However, to prove the invasion of the virus to CNS, the analysis of CSF for SARS-CoV-2 was not performed in these studies. Further, a study reporting a case of generalized-tonic clonic seizure and convulsive syncope due to autonomic dysfunction in patients later were found to have COVID-19, has supported this opinion. CSF samples analyzed did not reveal the presence of SARS-CoV-2 [87,88]. Interestingly, COVID-19 was seen to aggravate epilepsy in 18% of people who were already having epilepsy and the number of seizures were greater during the COVID-19 phase in comparison to the non-COVID-19 phase [89]. Yet, it is still unclear whether COVID-19 amplifies epilepsy or not [77]. Although these studies suggest that seizure might be an initial symptom associated with SARS-CoV-2, additional studies with larger samples are required in this regard.

4.2. Guillain-Barré Syndrome (GBS)

The GBS is an autoimmune neurologic disease of the peripheral nervous system caused by an infection of mainly the gastrointestinal or respiratory system leading to an autoimmune response towards antigens that cause demyelination and injury to the axons [90]. It is characterized by areflexia in the limbs, bilateral weakness in the facial muscles, bladder or bowel dysfunction, acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, etc. [91]. Viral epidemics such as the Zika virus, middle east respiratory syndrome coronavirus (MERS-CoV), SARS-CoV have triggered GBS [92–94]. Evidence proposes that through a resemblance of epitope mechanism, a cellular and humoral immune response to the virus is misdirected to host nerve tissue leading to GBS [95]. GBS is one of the neurological disorders in COVID-19 patients that causes many negative consequences for patients. Studies of COVID-19 patients diagnosed with GBS are summarized in Table 1.

The GBS diagnosis was based on clinical, CSF, electrophysiology, and nerve conduction studies. Intravenous immunoglobulin (IVIG) was injected in most of the studies. Yet, plasmapheresis was considered in two cases. Out of these cases, eleven studies used RT-PCR assay of the CSF to confirm the presence of SARS-CoV-2. However, the test was negative for SARS-CoV-2. Further, the absence of antibodies against gangliosides was observed in nine studies (Table 1). While these observations may primarily support the hypothesis that the disease itself may perhaps predispose patients with COVID-19 to GBS, the interpretation of these studies is complicated by the effect of SARS-CoV-2, which might differentially modulate the nervous system in COVID-19 patients with and without GBS. Several pieces of evidence point to the hypothesis that exposure of SARS-CoV-2 to the nervous system may result in abnormal activation of the immune system [96]. It has been proposed that viruses might provoke GBS by occupying glycoconjugates. Glycoconjugates, particularly gangliosides, are the neural targets for viruses [97]. As an attachment factor for cell entry, SARS-CoV-2 uses sialic acids [98]. The S proteins mediate the association and access of virions in target cells, and it has two components, namely the S1 subunit and S2 subunit as mentioned previously in Section 3. Sialic acids are linked to gangliosides [99]. Several gangliosides contribute to communications between axons and glia, receptor signal transduction, and growth [100]. Gangliosides usually are present on the plasma membrane of cells, rendering them vulnerable to an antibody-mediated attack [97]. It has been revealed how SARS-CoV-2 may disrupt the inflammatory cytokine system causing cytokine storm in COVID-19 [101]. This suggests that COVID-19 patients, in general possibly will be predisposed to neurological disorders like GBS [102,103]. Nevertheless, we would take into the reason that only a lesser number of COVID-19 patients develop GBS [104,105]. Therefore, more studies are desirable to evaluate the difference between COVID-19 patients who do develop GBS and the rest of the COVID-19 population.

4.3. Viral encephalitis

Encephalitis is an inflammation occurring in the brain that results in a neurological dysfunction due to infection or autoimmunity [91]. Generally, patients present with low levels of consciousness, seizures, fever, arthralgia, GI symptoms, and even respiratory malfunctions [116]. It is also characterized by the presence of inflammatory lesions in the brain parenchyma and is a clinical feature of COVID-19 sometimes coexisting with meningitis [117,118]. Even though this is an uncommon manifestation; there are reports of patients with COVID-19 diagnosed with encephalitis [118,119]. The underlying mechanisms responsible for encephalitis in SARS-CoV-2 are still debated. Classically, SARS-CoV-2 affects the respiratory system and cardiovascular system largely. Nevertheless, taking into deliberation the fact that encephalitis is present in SARS-CoV-2 infection at comparatively early stages when the central neuronal pathway is considered relatively spared, the other organ systems being involved may not be the only responsible. Viral intrusion into the CSF of a SARS-CoV-2 patient admitted for encephalitis has supported this hypothesis [120]. Currently, some authors have proposed that encephalitis might be the result of anti-NMDA (*N*-methyl-D-aspartate) receptor antibodies, causing functional disruption of glutamatergic signaling in the CNS [121]. On this point, it was suggested that immunologic responses in the brain, by influencing the glial system might lead to neuroinflammation and consequently encephalitis [3,122,123]. However, the observation that the presence of ACE2 receptor in the vascular endothelium which often correlates with clotting and infarction suggests an involvement of other mechanisms as well [124].

4.4. Meningoencephalitis

The meningoencephalitis occurs due to the inflammation of the meninges and the brain. It is evident by the symptoms like neck muscle rigidity, high temperatures, and headache probably due to meningeal inflammation. It could even cause inflammation in the brain parenchyma leading to cortical dysfunction and aphasia along with hemiparesis [125]. COVID-19 is associated with meningoencephalitis [25,126]. SARS-CoV-2 was detected in the CSF of a COVID-19 infected patient with meningoencephalitis [17]. The absence of an effective host immune defense system in the CSF allows pathogens to multiply rapidly. A paucity of complement proteins and immunoglobulins in the CSF prevents the phagocytosis of pathogens [127]. The common MRI findings described are white matter hyperintensities, the abnormal findings of the medial temporal lobe, and sulcus hemorrhage. Several observations have been suggested to explain the meningoencephalitis phenomena in COVID-19 patients. Increased levels of pro-inflammatory cytokine IL-6, ferritin, and high protein levels in CSF without pleocytosis may all be considered potential reasons [117]. The inflammatory response induced by the invading virus is a critical result of the pathogenesis of viral meningitis. Most of the neurologic manifestations of meningoencephalitis result from an immune-mediated reaction to the assaulting virus [127].

Table 1
Studies evaluating SARS-CoV-2 in CSF and antiganglioside antibodies in COVID-19 patients diagnosed with GBS

Study	Type of study	No. of cases	GBS diagnosis	RT-PCR assay SARS-CoV-2 in CSF	Anti-ganglioside antibodies	Treatment
[27]	Case Series	5	Clinical + CSF + Electrophysiology + Nerve conduction	Negative	3 negative; 2 not tested	IVIG
[106]	Case Series	14	Clinical + CSF	Negative	Not tested	IVIG and Plasma-pheresis
[107]	Case Report	1	Clinical + CSF + Electrophysiology + Nerve conduction	Negative	Negative	IVIG
[108]	Case Report	1	Clinical + CSF + Nerve conduction	Negative	Negative	IVIG
[109]	Case Report	1	Clinical + CSF + Nerve conduction	Negative	Negative	IVIG
[26]	Case report	1	Clinical + CSF + Nerve conduction	Negative	Negative	IVIG
[110]	Case Report	1	Clinical + CSF + Electrophysiology + Nerve conduction	Negative	Not tested	IVIG
[111]	Case Report	1	Clinical + CSF + Electrophysiology + Nerve conduction	Negative	Not tested	IVIG
[112]	Case Report	1	Clinical + CSF + Nerve conduction	Negative	Not tested	IVIG
[113]	Case Report	1	Clinical + CSF	Negative	Not tested	Low dose prednisolone
[114]	Case Report	1	Clinical + CSF + Electrophysiology + Nerve conduction	Negative	Negative	IVIG Hydroxychloroquine + Azithromycin
[115]	Case Report	1	Clinical + CSF + Electrophysiology + Nerve conduction	Not performed	Negative	Plasma exchange

4.5. Acute cerebrovascular disease (ACVD)

ACVD includes the diseases of the cerebral blood vessels, the flow of the cerebral blood, and the supply of oxygen to cerebral regions. Its main indication is the ischemic stroke that is caused due to blockage of cerebral blood flow and thus reduced oxygen supply [128]. The patients with severe COVID-19 infection are suspected of having ACVD, possibly due to higher D-dimer levels than non-severe COVID-19 patients [48]. During the activation of the coagulation system, a peptide degradation product is found circulating in the bloodstream named D-dimer. Higher levels of D-dimer in the systemic circulation could hint about higher changes of thrombosis, leading to stroke [129]. A recent study reported that COVID-19 patients could experience such activation of the coagulation system along with the increase in markers like hypersensitive C reactive protein (hsCRP), procalcitonin (PCT), Erythrocyte Sedimentation Rate (ESR), and D-dimer levels [130]. A systematic review by Sakka et al. showed that six studies that enrolled COVID-19 patients were grouped as survivors and non-survivors and interestingly the non-survivors exhibited high D-dimer levels, thus correlating to the cause of mortality in such patients [131]. Zhang et al. also showed that high D-dimer levels in COVID-19 patients could also be associated with a greater incidence of ischemic stroke as compared to hemorrhagic stroke [129]. Recently a study involving a comparison of older and comparatively younger COVID-19 infected patients showed that increased inflammatory response, neutrophil count, CRP levels, and D-dimer levels but lower lymphocyte count were exhibited by the older age group implying that older patients could be at higher risk of ACVD [132]. SARS-CoV-2 besides affecting ACE2 receptors in lung cells may also infect ACE2 receptors on endothelial cells causing endothelitis that could throw a light on the damage to microcirculation in vascular groups leading to ACVD [133]. Still, the exact mechanism of how SARS-CoV-2 mediates the risk of ACVD is unknown, thus demanding further studies.

4.6. Respiratory failure

Respiratory failure is caused mainly due to the improper functioning of the pump of respiratory muscle or lung dysfunction. While the cases of respiratory pump failure mainly include chronic obstructive pulmonary disease (COPD) patients, the conditions of lung damage arise in ARDS patients [134]. Animal studies have shown that SARS-CoV particles could gain entry into the brain via olfactory nerves and disseminate into the brain stem and even thalamus [135]. Interestingly, ACE2 receptors have been mapped in regions of the brainstem, in the paraventricular nucleus (PVN), in the nucleus of the tractus solitarius (NTS), and also in the rostral ventrolateral medulla [136]. The nucleus of the solitary tract in combination with nucleus ambigus together controls the inhalation and exhalation processes in the host [137]. The respiratory tract and lung regions contain mechanoreceptors and chemoreceptors that transmit sensory data into the solitary tract nucleus and nucleus ambigus and the innervations of efferent fibers arising from both leads into the respiratory system [138]. SARS-CoV-2 possibly travel towards the solitary tract nucleus neurons in the medulla oblongata and cause damage to the rhythmic respiration and action potentials in neurons which regulate processes of inspiration and expiration [139]. The brain stem contains a primary oscillator named as pre-Botzinger complex (PBC) which is the most crucial player in respiration. It also contains the retrotrapezoid nucleus or the parafacial respiratory group (RTN/pFRG) as the secondary oscillator. It is speculated that SARS-CoV-2 could penetrate the CNS and infect PBC [140]. This could lead to cardio-respiratory impairments responsible for causing ARDS in SARS-CoV-2 infected patients causing respiratory failure [141].

5. Conclusion

COVID-19 has resulted in millions of deaths across the world. During its initial outbreak, we were only aware of its peripheral symptoms like fever, headache, cough, respiratory difficulties, loss of appetite, diarrhea, etc. Neurological disorders such as seizures, viral encephalitis, meningoencephalitis, Guillain-Barré syndrome, acute cerebrovascular disease, and respiratory failure are quite common and represent a significant problem in the management of COVID-19 patients. In the last few months, several efforts have been made to clarify the role of the nervous system in these complications. Nevertheless, the results of the above studies have revealed that SARS-CoV-2 has infiltrated into the CNS through various routes. Upon the attachment of SARS-CoV-2 S protein to the ACE2 receptor, it enters the host and starts proliferating. CSF is an excellent marker of changes in CNS and accessing the CSF could be indicative of the presence of SARS-CoV-2 in CNS. While the role of the nervous system has been proposed, nevertheless, the complexity of neuronal networks prevents a clear understanding of the impact of SARS-CoV-2 on the various neurological symptoms. Currently, less focus lies on the CNS manifestations of SARS-CoV-2 as comparatively lesser cases are being evaluated in this direction. Even though certain findings have reported such conditions in COVID-19 patients, the exact mechanism of CNS infection remains speculative,

and further study is necessary to draw concrete conclusions regarding COVID-19 and its effects on CNS.

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CRediT authorship contribution statement

Sairaj Satarker and Madhavan Nampoothiri contributed to the study conception and study design. Data collection, analysis, was done by Sairaj Satarker and Madhavan Nampoothiri. Development of figures and tables was performed by Sairaj Satarker. Writing the original draft, article editing, and approval of final article by Madhavan Nampoothiri. All authors read and approved the final manuscript and taken due care to ensure the integrity of the work.

Declaration of competing interest

All authors declare that they do not have any conflict of interest in this study.

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