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# CNS implications of COVID-19: a comprehensive review

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**Abstract:** COVID-19 was first reported in December 2019 in the Wuhan city of China, and since then it has spread worldwide taking a heavy toll on human life and economy. COVID-19 infection is commonly associated with symptoms like coughing, fever, and shortness of breath, besides, the reports of muscle pain, anosmia, hyposmia, and loss of taste are becoming evident. Recent reports suggest the pathogenic invasion of the SARS-CoV-2 into the CNS, that could thereby result in devastating long term complications, primarily because some of these complications may go unnoticed for a long time. Evidence suggest that the virus could enter the CNS through angiotensin-converting enzyme-2 (ACE-2) receptor, neuronal transport, haematogenous route, and nasal route via olfactory bulb, cribriform plate, and propagates through trans-synaptic signalling, and shows retrograde movement into the CNS along nerve fiber. COVID-19 induces CNS inflammation and neurological degenerative damage through a diverse mechanism which includes ACE-2 receptor damage, cytokine-associated injury or cytokine storm syndrome, secondary hypoxia, demyelination, blood–brain barrier disruption, neurodegeneration, and neuroinflammation. Viral invasion into the CNS has been reported to show association with complications like Parkinsonism, Alzheimer’s disorder, meningitis, encephalopathy, anosmia, hyposmia, anxiety, depression, psychiatric symptoms, seizures, stroke, etc. This review provides a detailed discussion of the CNS pathogenesis of COVID-19. Authors conclude that the COVID-19 cannot just be considered as a disorder of the pulmonary or peripheral system, rather it

has a significant CNS involvement. Therefore, CNS aspects of the COVID-19 should be monitored very closely to prevent long term CNS complications, even after the patient has recovered from COVID-19.

**Keywords:** CNS complications; coronavirus; COVID-19; neurodegeneration; neuroinflammation; SARS-CoV-2.

## Introduction

Corona Virus Disease-2019 (COVID-19) or the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in the Wuhan city of China in December 2019, and since then it has exploded uncontrollably all over the world taking a heavy toll on life and economy (Kong et al. 2020; Li et al. 2020b). Initially, it was recognized as a potential cause of unexplained and untreated pneumonia; however, it was later identified as COVID-19 (Sohrabi et al. 2020). The novel human coronavirus, SARS-CoV-2, primarily invades the respiratory system, which is diagnosed by the oropharyngeal and nasopharyngeal swab test (Thoms et al. 2020). The incubation period ranges from 1 to 12.5 days but can be extended up to 14 days for symptoms to appear (Liao et al. 2020). A bigger threat is the alarming surge of asymptomatic COVID-19 patients, which severely threatens the preventive measures currently undertaken by nations all over the world. Clinically, COVID-19 is associated with cough, fever, shortness of breathing, and ultimately compromise the respiratory system (Repici et al. 2020). As of 14th September 2020, COVID-19 has resulted in more than 28.9 million cases and more than 9.25 lac deaths worldwide WHO (2020) (Retrieved on 14th September 2020).

The higher incidences of lower respiratory tract COVID-19 infections are witnessed in neonates, elderly and persons with primary illnesses (Guo et al. 2020). Emerging evidence in the past few months suggests that COVID-19 can attack various body systems including the CNS (Moriguchi et al. 2020). Reports suggest that approximately 36.4% of COVID-19 patients develop some sort of neurological complications (Wu et al. 2020). On March 4, 2020, in Beijing Ditan Hospital, the first case of viral encephalitis showed the potential of SARS-CoV-2 to invade CNS (Xiang et al. 2020; Zhou et al. 2020b). It is now evident that SARS

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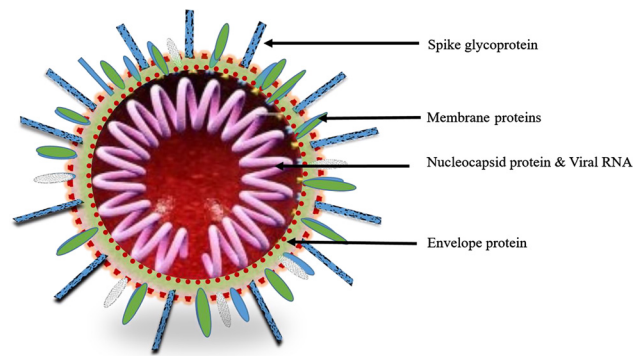
CoV-2 interacts with the human angiotensin-converting enzyme-2 (ACE-2) which is widely distributed not only in the epithelial cells of lungs but also the endothelial cells of the Blood-Brain-Barrier (BBB). These observations and previous research on SARS virus suggest that it can have a devastating effect on the brain too (Briguglio et al. 2020; Kuba et al. 2005; Ji-Young et al. 2020). Moreover, brain tissue edema and partial neuronal degeneration were observed in the autopsy reports of deceased patients (Wu et al. 2020). Furthermore, many patients suffering from COVID-19 infection experience the symptoms of loss of taste and smell, which are well-established CNS functions, indicating that the virus can directly affect the olfactory functions of the CNS (Izquierdo-Dominguez et al. 2020). Various studies also indicate the nonspecific involvement of SARS-CoV-2 with nervous system tissues, which may go unnoticed and cause severe damage in the CNS (Ahmed et al. 2020).

Currently, there is no vaccine or curative treatment available against this virus. The proposed review will highlight the recent advancement in the COVID-19 research with particular emphasis on the CNS, and possible potential therapeutic strategy for the management of complications associated with COVID-19.

## Coronavirus (CoV)

Coronavirus (CoV) is either pleomorphic or spherical, characterised by bear's club-shaped projections of glycoproteins having diameter 80–120 nm (Yang et al. 2006). Amongst all the RNA viruses, a single-stranded RNA genome of CoV is one of the most prevalent form sizes ranging from 26.2 to 31.7 kb (Chen et al. 2020a, b). The number of open reading frames (ORFs) in the CoV genome ranges from 6 to 10 (Belouzard et al. 2012). CoV genetic material is vulnerable to common recombination processes, which can give rise to new strains with alteration in virulence (Thomas and Nielsen 2005). Human CoVs, have seven strains which include 229E, NL63, OC43, HKU1, Middle East respiratory syndrome (MERS)-CoV and novel SARS-CoV-2, responsible for causing the respiratory tract complications like pneumonia, bronchiolitis, pharyngitis, common cold and sinusitis (Chang et al. 2016; Paules et al. 2020).

Structurally, CoV is made up of proteins such as spike protein, membrane protein, envelope protein and the nucleocapsid protein (Figure 1) (Gu and Korteweg 2007; Guo et al. 2008). Some strains of CoV strains express one additional envelop-associated protein, the hemagglutinin-esterase (HE) protein (Li 2016). The CoV RNA genome is packed in the nucleocapsid protein and further covered with the envelope (Guo et al. 2008). The CoV envelope is



**Figure 1:** Diagrammatic representation of the SARS-CoV-2 structure.

dotted with glycoproteins, and membrane proteins surrounding a core enclosing the single-stranded RNA present in association with nucleoprotein. The spike proteins are responsible for attachment and invasion of the CoV into the host cell by interacting with ACE-2 (Hilgenfeld 2014). The RNA genome has seven genes (ORF1A, ORF1B, ORF3, E, M, S, and N) in 5' to 3' direction (McBride et al. 2014). The ORF1A and ORF1B genes, which cover two-thirds of the genome, produce two viral replicase polypeptides (*pp1a* and *pp1ab*). These replicase polypeptides are then involved in the production of sixteen nonstructural proteins (Li 2016). The remaining one-third genome codes for the structural proteins (spike, envelope, membrane and nucleocapsid) and other accessory proteins (McBride et al. 2014).

In humans, three strains namely SARS-CoV, MERS-CoV, and SARS-CoV-2 are known to be rare but extremely pathogenic (Al-Osail & Al-Wazzah 2017; Saif 2004). The two well-known viral outbreaks are the SARS-CoV outbreak (2003) in the Guangdong province of China and the MERS-CoV outbreak (2012) in Saudi Arabia (Al-Osail & Al-Wazzah 2017; Saif 2004).

Structurally, SARS-CoV-2 primarily consists of four major proteins, along with several other assessor proteins, which makes up the structure of this virus. These four major proteins includes small envelope (E) glycoprotein, nucleocapsid (N) protein, spike (S) glycoprotein and membrane (M) glycoprotein (Jiang et al. 2020). Among these proteins, the S-glycoprotein is 150 kDa transmembranous protein, structurally located on the outer part of SARS-CoV-2. This S-glycoprotein of SARS-CoV-2 is having a strong affinity towards ACE2 receptor of the host cells and thereby facilitate the binding of the virus to the host cell expressing ACE 2 receptors. The furin-like protease present in the host cells cleave S-glycoprotein into S1 and S2, amongst which S1 functions primarily as the receptor binding domain and S2 facilitates the fusion of the

SARS-CoV-2 into the host cell (Fehr et al. 2015; Guo et al. 2020; Walls et al. 2020). Further, M-protein is responsible for the determining the structural integrity and the shape of the virus envelope. M-protein is having the potential to bind with other structural proteins which help in stabilizing these proteins. For example, M-protein stabilizes the nucleocapsids or N proteins and thereby facilitates the viral assembly inside internal virion by stabilizing N protein-RNA complex. E-protein or the envelop protein is the smallest structural protein of the SRAS-CoV-2 and is essential for SARS-CoV-2 production and maturation (Schoeman and Fielding 2019).

## The life cycle of the virus in the host cell

Humans and several animals including cattle, cats, bats, and camels may serve as hosts for CoVs (Cui et al. 2019). In humans, SARS and MERS are the two most pathogenic and mainly spread through respiratory droplets transmission (coughs or sneezes), close contact with an infected person, and through contaminated objects; besides, recent evidence of the aerosol transmission has gained importance (Adhikari et al. 2020). It can also spread through sweat, stool and urine (Ding et al. 2004). The principal target of the SARS-CoV is epithelial cells of the lungs. The other major target cells of CoV are enterocytes, pneumocytes, immune cells, neurons, and renal tubular epithelial cells (Guo et al. 2008).

CoV invades the target cells with the help of spike protein–host cell ACE-2 interaction in SARS-CoV (Zhang et al. 2020b) and dipeptidyl peptidase-4 (DPP-4) in MERS-CoV (Mubarak et al. 2019). Besides, the virus also needs a cofactor transmembrane serine protease 2 (TMRSS2) that activates the entry of the virus into the host cell followed by infection and replication (Antalis et al. 2010). The virus genome is released inside the host cell and its viral replicase polyproteins (*pp1a* and *pp1ab*, coded by ORF1A and ORF1B genes) help to take command over host ribosomes for their own translation process (Prajapat et al. 2020).

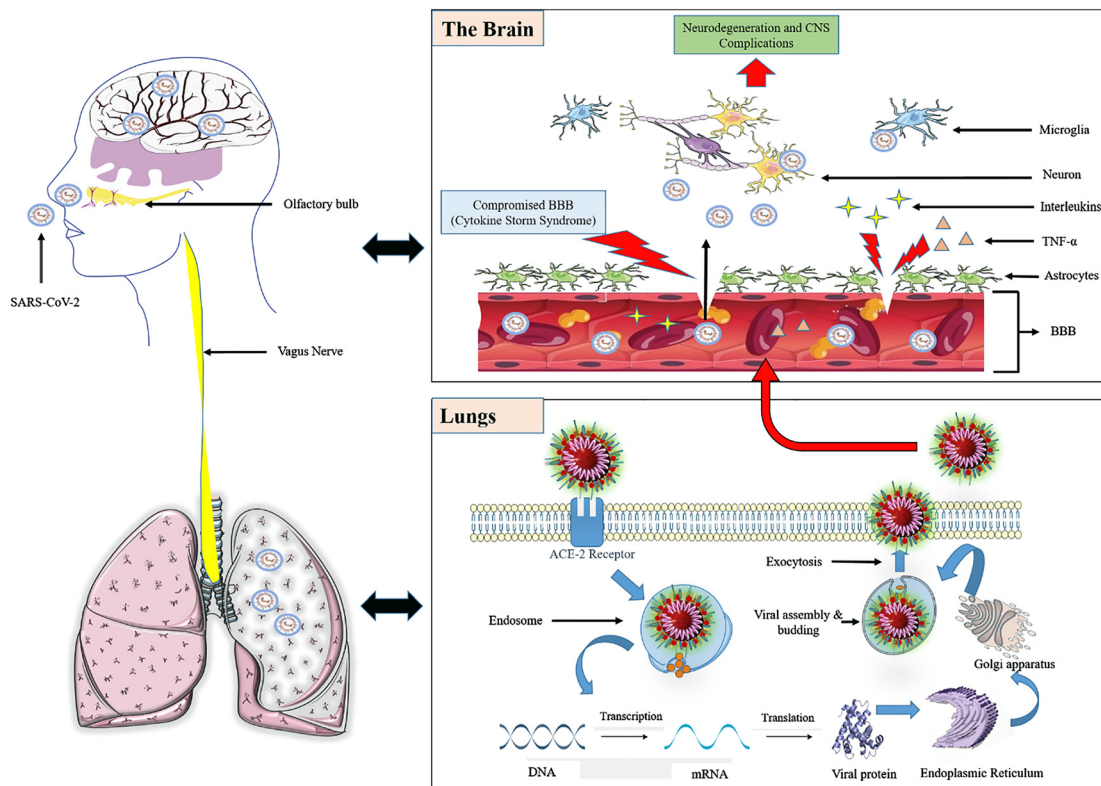
When viruses enter into the body through respiratory or other routes, the virus spikes binds to the ACE2 receptors of target cells (Desforges et al. 2014). It has been found that the novel CoV spike proteins provide the virion with many folds higher binding affinity to the host cell membrane than that of the SARS CoV spike protein (Vabret et al. 2020), and thus the novel CoV 19 has higher virulence than traditional SARS CoV Figure 2.

The host immune system, in response to the CoV, gets activated and releases the inflammatory cytokines

in the systemic circulation (Ding et al. 2004). The release of cytokines and other immune cells such as lymphocytes and neutrophils further cause inflammation, fever, decrease in pH of the blood and pleural outflow, which eventually leads to lung injury (Guzik et al. 2020). Also, showing consistency with the cytokine release syndrome, dysregulation of the pro-inflammatory cytokine pathway, specifically involving IL-6 and TNF- $\alpha$ , was reported in the cerebrospinal fluid (CSF) of critically ill COVID-19 patients (Krett et al. 2020). Moreover, the inflammatory mediators damage the BBB and increase its permeability, making CNS vulnerable to complications like neuroinflammation, encephalitis (Erickson et al. 2012).

After entry into the host cells, virus triggers the host immune response. Initially, the virus is encountered by the antigen-presenting cells (APC) such as macrophages and dendritic cells, which are the components of the innate immune system (Rabi et al. 2020; Li et al. 2020a). Pattern recognition receptors (PRR) of the APC, such as RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), toll-like receptors (TLRs), etc., recognize either the structural components such as carbohydrate moieties, nucleic acids, lipoproteins, glycoproteins and other proteins present on the virus or recognise the intermediate products of the virus such as RNA, dsRNA, etc. to initiate the immune signalling cascade. Moreover, each PRR is capable of triggering different reaction based on the activation and recognition of the viral components (Li et al. 2020a; Yi et al. 2020). Further, with the help of the MHC class 1, APC present the coronavirus antigen to the CD4<sup>+</sup> helper T-cell. This leads to the release of proinflammatory cytokines such as IL-12, IL-17, and INF- $\alpha$ , which further enhance the expression and activates MHC class 1 and NK cell. This is crucial for countering the viral replication within the host cell and eliminating the infected cells. This further activates the NF- $\kappa$ B signaling pathway that triggers the activation and release of proinflammatory cytokines. These cytokines attracts monocytes and neutrophils to the infection site and leads to the activation of several other proinflammatory cytokines and chemokines such as TNF- $\alpha$ , MCP-1, IL-1, IL-6, IL-8 and IL-21 (Janeway et al. 2008; Li et al. 2020a; Rabi et al. 2020; Zumla et al. 2020).

The activation of the CD4 cells stimulates the humoral response against the virus and aids in the generation of the antibodies against the coronavirus, which mainly consists of IgM and IgG (Janeway et al. 2008; Li et al. 2020b; Rabi et al. 2020). COVID-19 generally generate specific IgM antibodies that lasts a duration of 12 weeks and IgG antibodies that last longer. Moreover, exposure of the



**Figure 2:** The mechanism of COVID-19 infection and pathway for CNS invasion and associated CNS complications.

The COVID-19 can invade CNS via disrupted BBB, through neuronal pathway and olfactory pathway. The primary mechanism of the CNS damage is by inflicting cytokine storm syndrome which not only damages neurons, but also disrupts the physiology of the BBB. Further, COVID-19 virus (SARS-CoV-2) utilize ACE-2 receptor for cellular invasion, multiplication and damages the lungs, causing hypoxia, which further adds to the COVID-19 mediated complications. ACE-2: Angiotensin-converting enzyme-2; BBB: Blood Brain Barrier; TNF: Tumor necrosis factor; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2.

coronavirus induce formation of CD4 T cells and CD8 memory, which could last upto four years (Fan et al. 2009).

## Routes of CNS invasion utilized by the virus

Many viruses are known to invade CNS such as HIV, influenza virus, flaviviruses, mouse adenovirus type 1, parainfluenza virus, lymphocytic choriomeningitis virus, arbovirus, cytomegalovirus, rhabdovirus mumps virus, parvovirus B19, measles virus, herpes simplex virus, human T-cell leukemia virus, enterovirus, morbillivirus, bunyaviruses, CoV and others (Michalíková et al. 2017; Takahashi and Suzuki 2011). However, the pathogenesis of CoV neuronal invasion was not fully understood. The first case of CSF positive COVID-19 was reported on March 4, 2020, in China through genome sequencing techniques (Al Saiegh et al. 2020). The CNS impediments have also been

observed from the autopsy reports of the COVID patients, which specify the severe degree of neurodegeneration and cerebral edema in the brain (Briguglio et al. 2020). Another case of neuroinvasive nature of the COVID-19 was observed in the brain tissue of a 74-year-old patient (Paniz-Mondolfi et al. 2020). Also, the occurrence of sphere-shaped viral spots in the endothelial cells with a distinct stalk-like projection was observed in the neural cell bodies (Paniz-Mondolfi et al. 2020). Researchers also established that the human protein neuropilin-1 (NRP-1) allows viral invasion. It was hypothesized that the CoV can bind to NRP-1, and the antibody that binds to this protein can block infection in the human cells. Experimental validation on mice revealed that NRP1 supports the entry of virus-sized particles into the CNS. The study suggested that interaction between the virus and host NRP1 could help to combat CoV infection (Daly et al. 2020).

Various studies indicate the specific or non-specific routes of the interaction of COVID-19 with the nervous system tissues, which has been discussed below.

## Neuronal transport

The SARS-CoV-2 can migrate to the CNS through the olfactory, respiratory, and enteric nervous system pathway (Esposito et al. 2020; Wu et al. 2020). Owing to the vicinity of the olfactory neurons and olfactory bulb with the brain, the virus transfers through the sensory or motor endings of the axonal neuron to the brain (Esposito et al. 2020; Wu et al. 2020). Besides, owing to the presence of ACE 2 receptors on olfactory cilia cells, the virus can reach the CSF within seven days (Wu et al. 2020). A study in mice by Bohmwald et al. (2018) suggested a restricted entry of CoV into the CNS when the olfactory bulbs were removed, thereby confirming that CoV can invade CNS via this pathway (Bohmwald et al. 2018).

The virus can also reach the medulla oblongata (respiratory centre), by the neurons which innervate and regulate the respiratory system (Baig 2020; Li et al. 2020b; Li et al. 2020c). The first CoV HEV 67N was known to invade the porcine brain via peripheral nerves. The transmission of HEV 67N between neurons has also been recognized by ultrastructural studies using clathrin-coating-mediated endocytotic and exocytotic pathway (Li et al. 2020b, 2020c).

The high availability of ACE-2 receptors in the enterocytes cells of the gut and direct connection of the enteric nervous system with the brain via vagus nerve provides an additional route for the entry of the virus to the brain (Gao et al. 2020). The SARS CoV2 can directly infect and replicate in the intestinal cells that further triggers a peripheral immune response such as the excess release of cytokines (Gao et al. 2020). This cytokine storm facilitates enteric inflammation and neuroinflammation in the brain and disruption in the intestinal barrier due to inflammation causing secondary systemic infection and viral translocation (Huang et al. 2020).

## Haematogenous route

The integrity of the CNS is protected by the combined efficiency of the BBB and the blood-CSF barriers, which restricts the entry of unwanted substances into the CNS. Our circulatory system is another potential pathway that SARS-CoV-2 can utilize to get entry into the CNS. In this pathway, infected epithelial cells release the virus from the basolateral side into the circulation, which can then spread to various organs. Since neurons are protected by the BBB, they are not in direct contact with the circulatory system, the virus spreads into the CNS from the circulation by utilizing intermediate host cell, viz. endothelium and

leukocytes (Koyuncu et al. 2013). Some virus like hepatitis E virus (Tian et al. 2019), HSV (He et al. 2020) and encephalitic alphaviruses (Salimi et al. 2020) can infect the epithelial cells of BBB from the circulation. This is followed by the release of inflammatory cytokines that disrupts the normal functioning of the BBB and increases its permeability, leading to CNS infection (He et al. 2020; Salimi et al. 2020; Tian et al. 2019). Considering the high expression of ACE2 receptor on the BBB epithelial cells, the possibility of COVID-19 to inflict BBB damage and CNS infection cannot be overlooked.

Other viruses such as HIV (Kaul et al. 2001) and Zika virus (Ayala-Nunez et al. 2019) utilise the “Trojan horse” mechanism to enter CNS in which they use leukocytes for transporting them across BBB (Gu et al. 2005; McGavern and Kang 2011). Virus such as HIV, accumulates in the monocytes which are capable of passing the BBB physically (Collman et al. 2003). They get entry to the CNS where they activate the microglia to secrete chemokines, leading to high degree of monocyte infiltration, enhanced BBB permeability and inflammatory process within the CNS (Eugenin et al. 2003; Persidsky et al. 2000). Coronavirus, such as HCoV-229E, are also known to infect leukocytes leading to accumulation in the monocytes and macrophages (Collins 2002; Desforges et al. 2007), invade dendritic cells (Mesel-Lemoine et al. 2012) and initiate the process of chemokine secretion (Spiegel et al. 2006), suggesting that the coronavirus could also utilize the “Trojan horse” mechanism to gain access into the CNS and infect it.

## Angiotensin-converting enzyme- 2 (ACE-2)

ACE-2 is a protein expressed in diverse tissues including the respiratory system, gastrointestinal system and the brain. ACE-2 is highly abundant in the type-2 pneumocytes, an important cell type present in the alveoli, where the exchange of oxygen and carbon dioxide occurs. It is essential for blood pressure control, normal cardiac function, and is an essential regulator of the rennin angiotensin system (RAS). CoV attack on the ACE-2 receptors can also affect the normal functioning of the RAS (Vaduganathan et al. 2020). Due to the presence of ACE-2 receptors in the neuron, viruses gain entry into the neurons and overtake cellular machinery (Buja et al. 2020; Xu and Lazartigues 2020). Spike-like protein on the surface of the virus binds to the ACE-2 receptors, which inhibits the normal neuronal functioning to regulate angiotensin II and the destruction of ACE-2 producing tissues (Buja et al. 2020). Previous studies reported that SARS-CoV-2 caused neuronal death in mice by invading the brain through the olfactory route

(Izquierdo-Dominguez et al. 2020; Wu et al. 2020). SARS-CoV-2 also shows its presence in the CSF (Al Saiegh et al. 2020; Wu et al. 2020). The potential binding of the viral spike protein with ACE-2 expressed in the capillary endothelial lining favours the viral entry to the brain, followed by a viral infection, replication, and then neuronal inflammation (Al Saiegh et al. 2020; Wu et al. 2020). It has been reported that firstly there is the endothelial damage in cerebral capillaries with bleeding in cerebral tissues followed by neuronal damage (Al Saiegh et al. 2020; Paniz-Mondolfi et al. 2020; Wu et al. 2020). Furthermore, angiotensin II stimulates the activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) in human monocytes, which initiates inflammatory signaling pathways. Further, ACE-2 protects the endothelial layers, and its deficiency was found to be associated with dysfunction in cerebral arteries of the adult mice (White et al. 2020).

### Cytokine storm syndrome in CNS

Neuroinflammation is one of the major pathways associated with the variety of the CNS complications. Recent findings suggest that the COVID-19 could inflict structural and metabolic damage in the CNS by upregulating inflammatory cytokines like TNF- $\alpha$ , IL-6 etc. This phenomenon is known as the cytokine storm syndrome. The development of the cytokine storm syndrome by COVID-19 or SARS-CoV-2 resembles other neurotropic viruses, which induce IL-6 surge from the glial cells, such as astrocyte and microglia, in the brain (Wan et al. 2020; Wu et al. 2020). Bohmwald et al. (2018) have demonstrated the association of the glial cells to induce chronic inflammation and brain damage by enhancing the levels of pro-inflammatory cytokines, such as IL-6, TNF- $\alpha$ , IL-5 and IL-2 through an *in-vitro* study (Bohmwald et al. 2018). Inside the CNS, SARS-CoV-2 activates CD4<sup>+</sup> cells that secrete IL-6 and activates the macrophages. Cytokine storm syndrome could lead to failure of multiple organs, which is the major cause of the mortality and morbidity during COVID-19 (Chen et al. 2020a). These findings are justified appropriately by the findings of the Zhang et al. (2020a), where they have demonstrated a significant improvement in a critically ill patient of COVID-19 after being treated with the IL-6 blocker, Tocilizumab (Zhang et al. 2020a). These findings, although raw, give clear-cut indication that the cytokine storm syndrome in CNS is one the major molecular pathway through which SARS-CoV-2 might induce damage to the brain.

## Coronavirus mediated CNS complications

Accumulated evidence from the literature suggests that the CoVs such as SARS-CoV, MERS-CoV and HCoV-229E has the potential to invade CNS and induce neuronal infections (Huang et al. 2020). Due to the striking structural resemblance of the SARS-CoV-2 with the SARS-CoV, the potential of SARS-CoV-2 to invade CNS and to inflict complications cannot be neglected (Andersen et al. 2020). The clinical reports propose that the virus could be neurotropic as patients go through neurological symptoms such as loss of taste (5.1%), loss of smell (5.6%), stroke and seizure (Mao et al. 2020a). Recently researchers found SARS-CoV-2 to be potent neurotropic by using an *in-vitro* 3D human brain organoids model, which resembled human CNS (Ramani et al. 2020). It was found that the virus targets the cortical neurons causing Tau hyperphosphorylation and cell death (Teixeira et al. 2020). Further, various studies have reported that COVID-19 patients show neurological symptoms such as headache, nausea, anorexia, myalgia, and vomiting, suggesting CNS implications of COVID-19 infection (Montalvan et al. 2020; Gupta et al. 2020).

### Neurodegenerative disorder

There is no conclusive evidence of whether COVID-19 patients suffer from a neurodegenerative disorder or not, but it is suspected. The Braak hypothesis of Parkinson's diseases proposed that the virus affects the main area in the brain such as substantia nigra which causes  $\alpha$ -synuclein to turn into a loose binder (Santos et al. 2019). It is also speculated that the disruption in the BBB as a result of COVID-19 associated cytokine storm syndrome may result in the progression of neurodegenerative disorder. The presence of proinflammatory mediators (IL-6 and TNF $\alpha$ ) have been found in the CSF and the brain tissues of the deceased patients of Parkinson's disease (Schwab et al. 2020). The presence of the proinflammatory mediators IL-1 and IL-6, which leads to the A $\beta$  deposition, supports the hypothesis that the neuroinflammation due to cytokine storm may lead to Alzheimer's disease (Serrano-Castro et al. 2020).

Accumulated evidence confirms the potential of the COVID-19 to invade CNS, however, its effects at the molecular and mechanistic levels have only been speculations and hypothesis. Some reports suggest that SARS-CoV-2 can

impair the functioning of the brain regions involved in neurodegeneration during Parkinsonism. These findings are supported by the symptoms of ageusia and anosmia (Lechien et al. 2020) during COVID-19, which are also the classic features of Parkinsonism (Rey et al. 2018a; Schirinzi et al. 2018). Interestingly, during the pathogenesis of Parkinsonism, Lewy bodies get accumulated in the olfactory pathway, from where its propagation to other regions of the brain along the olfactory system connections occurs, causing neuronal degeneration (Rey et al. 2018a; Schirinzi et al. 2019). This overlap between the CNS penetration of the COVID-19 and Parkinsonism becomes more critical, considering that some patients of COVID-19 may completely lose the sense of smell and many recover partially (Lechien et al. 2020a), suggesting the potential neuronal injury in this region which could initiate synucleinopathy cascade (Rey et al. 2018b). This, along with inflicting neuroinflammation via cytokine storm syndrome, COVID-19 could enhance the risk for the development and progression of Parkinsonism (Krashia et al. 2019). Moreover, the blood inflammatory profile of the COVID-19 patients suggests a significant increase in the IL-2R, IL-6, IL-8, IL-10, ferritin and C-reactive protein (Henry et al. 2020). This increase in the inflammatory profile is interesting since enhanced levels of C-reactive protein, IL-1 $\beta$ , IL-2, IL-6 and TNF are also observed in the blood samples of the patients suffering from Parkinsonism (Qin et al. 2016; Qiu et al. 2019), besides, demonstrating high degree of correlation with the clinical severity (Maass et al. 2019). It is being speculated that the neurological complications in which inflammation plays a crucial role, such as multiple sclerosis, narcolepsy, Alzheimer's Disorder etc., could show high degree of association with the COVID-19 (Schirinzi et al. 2020). Evidence generated so far suggests that the psychiatric comorbidity of COVID-19 cannot be neglected. COVID-19 patients have been observed to develop anxiety and depression; however, this could not be solely attributed to COVID-19 due to lack of conclusive evidence (Rogers et al. 2020).

## Intracranial infections

COVID-19 patients suffer from severe hypoxia which causes pulmonary, metabolic disorders and encephalopathy (Wu et al. 2020). Influenza and viral infections have been related to the cytokine storms and neuronal demyelination (Jang et al. 2009). Recently the first case of acute necrotizing hemorrhagic encephalopathy with COVID-19 was reported (Pryce-Roberts et al. 2020). In the meningeal inflammation autopsy report of the COVID-19 patients, increased levels of IFN, TNF, IL-2 and IL-22 were observed accompanied by

increased B-cell activity (Serrano-Castro et al. 2020). These reports also support the role of neuroinflammation in the CNS-related diseases (Machhi et al. 2020). Due to the absence of the clinical data, it is not clear whether inflammation is the lone factor underlying neuronal death or some other factors are involved too. The loss of taste and smell has now been observed as a symptom of COVID-19 infection (Lao et al. 2020). Lechien and colleagues reported olfactory dysfunction in 357/417 and anosmia in 342/417 COVID-19 patients. It has been suggested that vagus and olfactory nerve infiltration by the virus are responsible for these symptoms (Lechien et al. 2020b).

**Encephalitis:** Viral infections are mainly responsible for encephalitis, also known as acute brain inflammation. The causative viruses mainly include *Varicella zoster* virus, influenza virus, *Herpes simplex* virus (HSV) and cytomegalovirus (Kennedy 2004); however, the etiology of SARS-CoV-2 and MERS-CoV have also been identified during encephalitis (Saad et al. 2014; Vandervorst et al. 2020; Babar et al. 2020). The presence of the SARS-CoV-2 RNA has been detected in the CSF in patients having the medical condition of clinical meningoencephalitis (Moriguchi et al. 2020). Similarly, a patient infected with COVID-19 has been diagnosed with an altered mental status, which was suspected due to the presence of encephalitis in the brain (Poyiadji et al. 2020). Encephalitis in this patient was not as a result of direct SARS-CoV-2 invasion into the brain, rather, it was because of the SARS-CoV-2 mediated cytokine storm syndrome. Similar studies suggest that the cytokine storm syndrome may be responsible for the variety of severe symptoms observed in the patients infected with COVID-19 (Mehta et al. 2020). These reports find some support from the clinical findings where the patients of COVID-19 who were administered IL-6 and IL-1R receptor inhibitors (tocilizumab and anakinra) showed some improvement in COVID-19 infection (Shakoory et al. 2016; Zhang et al. 2020a).

**Viral meningitis:** COVID-19 associated meningitis was firstly reported in a young patient from Japan who demonstrated altered consciousness and seizure episode (Moriguchi et al. 2020). He was diagnosed with encephalitis of the right mesial lobe and hippocampus along with the right lateral ventriculitis. Interestingly, this patient was tested positive for the SARS-CoV-2 RNA in the CSF; however, it was not diagnosed through a nasopharyngeal swab test. These findings suggest the neuroinvasive potential of SARS-CoV-2 or COVID-19 (Moriguchi et al. 2020).

## Neuropsychiatric disorders

Accumulated evidence in recent past suggests that COVID-19 could be associated with psychiatric symptoms. Hu et al.

(2020) reported an increased incidence of the first episode of schizophrenia and COVID-19 (Hu et al. 2020). It has also been observed that 96% of recovered COVID-19 patients show posttraumatic stress symptoms (Bo et al. 2020). A retrospective study on 58 COVID-19 patients showed psychiatric and neurologic signs such as confusion (65%), corticospinal tract symptoms (67%), and neuropsychological impairment (33%) (Helms et al. 2020). A systemic study on more than 900 patients shows the association symptoms such as confusion and impaired consciousness with COVID-19 (Rogers et al. 2020). Moreover, a study on 144 patients suggests anxiety (35%) and depression (28%) association with COVID-19 (Rogers et al. 2020). United Kingdom-based surveillance study conducted by Varatharaj et al. (2020) reported altered mental status in 59% COVID-19 patients, of which majority of the cases were newly diagnosed. They further reported that amongst patients diagnosed with altered mental status, 43% cases were of new-onset psychosis, 26% patient demonstrated neurocognitive or dementia-like manifestations, 17% were observed to have affective disorder (Varatharaj et al. 2020).

## Anosmia

Anosmia and hyposmia are associated with COVID-19 (Vaira et al. 2020), which can be present in patients before other symptoms are noticed (Eliezer et al. 2020). A retrospective study conducted on 114 patients of COVID-19 demonstrated the presence of anosmia in 47% of patients (Klopfenstein et al. 2020). Moreover, this study demonstrated that anosmia appears approximately 4.4 days after COVID-19 and has an overall duration of 8.96 days. Moreover, 98% patients of COVID-19 were reported to recover within 28 days of the infection (Klopfenstein et al. 2020). Anosmia is the most prevalent CNS manifestation of the COVID-19 or the SARS-CoV-2 infection. Interestingly, anosmia is diagnosed in asymptomatic patients and patients in the early 20s age group (Lao et al. 2020). COVID-19 patients can have a sudden onset of anosmia without having any other typical symptoms of the infection, however (Gane et al. 2020), some patients may show the symptoms of mild dry cough (Eliezer et al. 2020). There have been multiple cross-sectional studies depicting the prevalence rate of anosmia and hyposmia in COVID-19 patients. These studies report a wide range of prevalence from 33.9 to 68% in COVID-19 patients (Bagheri et al. 2020; Giacomelli et al. 2020; Menni et al. 2020; Spinato et al. 2020; Yan et al. 2020). These studies also highlighted the association of anosmia with the taste disorder in these patients (Bagheri et al. 2020; Giacomelli et al. 2020; Menni et al. 2020; Spinato et al. 2020; Yan et al. 2020). Interestingly, in most of the study the prevalence of the olfactory disorders were observed to be

higher in females when compared to males (Bagheri et al. 2020; Giacomelli et al. 2020; Spinato et al. 2020).

## Vascular events (CVA/AIS)

Etiology of the acute ischemic stroke (AIS) associated with the COVID-19 has not been fully understood; however, there are reports which suggest that ischemic stroke could be associated with the severe COVID-19. Retrospective studies conducted on the hospitalized COVID-19 patients in China and Europe suggest a stroke incidence rate of 2.5–6% in COVID-19 patients (Klok et al. 2020; Lodigiani et al. 2020; Mao et al. 2020b). Interestingly, AIS has also been reported to be associated with the SARS and MERS epidemics, suggesting that association of AIS with COVID-19 cannot be neglected (Algahtani et al. 2016; Umaphathi et al. 2004). This association was also reported recently in a case series from New York where five patients of COVID-19 developed large-vessel ischemic strokes, with elevated inflammatory markers and symptoms like acute stroke symptoms and lymphopenia (Oxley et al. 2020).

Recent reports suggest that the COVID-19 patients could be at higher risk of developing thromboembolic adverse events (Guan et al. 2020; Klok et al. 2020; Zhou et al. 2020a). Severe COVID-19 patients has demonstrated enhanced coagulation activity that was associated with the elevated D-dimer concentrations (Guan et al. 2020; Klok et al. 2020) that even led to fatality (Zhou et al. 2020a). Further, it has also been reported that the patients with both COVID-19 and cerebrovascular disease were having higher D-dimer levels than those without cerebrovascular disease (Klok et al. 2020), suggesting the association of COVID-19 with higher D-dimer levels and associated complications. Moreover, endotheliitis could result as a consequence of viral invasion through ACE-2 receptor and subsequent inflammatory reaction, thereby contributing to variety of clinical etiology of COVID-19 (Varga et al. 2020). Endotheliitis could result in the endothelial dysfunction and microcirculatory vasoconstriction leading to apoptosis and ischemia (Varga et al. 2020).

Mao et al., reported a stroke incidence rate of 3% in hospitalized COVID-19 patients (Mao et al. 2020a). Likewise, Strasbourg University Hospital the development of cerebral ischemic stroke in three patients out of 23 investigated (23%) (Helms et al. 2020). A single-center retrospective study was conducted on 221-hospitalized COVID-19 patients in China. This study demonstrated 13 cases of acute strokes consisting of 1- hemorrhagic, 1- venous sinus thrombosis and 11-ischemic strokes (Li et al. 2020d). Although a direct evidence linking COVID-19 to the AIS has not yet been established, recent

reports suggest that COVID-19 could be associated with the higher incidence of AIS and should be closely monitored during the management of COVID-19 patients.

## Myelitis

Mao et al. (2020a) were amongst the first scientists to report neurological manifestations in 36.4% (78/214) of COVID-19 patients. Headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy were the most reported cases of neurological manifestations of COVID-19 (Mao et al. 2020a). Several case reports have now observed an association of COVID-19 with acute transverse myelitis (ATM). Sarma and Bilello (2020), Valiuddin et al. (2020), and Zhao et al. (2020a) reported the first three cases of acute myelitis post SARS-CoV-2 infection. More studies confirming this association has started to emerge as the pandemic progresses globally (Hazrati et al. 2020; Munz et al. 2020; Sotoca and Rodríguez-Álvarez 2020). Recently, a case report showed a SARS-CoV-2 and myelin oligodendrocyte glycoprotein (MOG) IgG antibody positive patient with bilateral severe optic neuritis and myelitis, suggesting a potential association of COVID-19 and myelitis (Zhou et al. 2020c).

Based on the extensive sequence homology and neuroinvasive potential of SARS-CoV-1, MERS-CoV and other coronaviruses, it has been hypothesized that SARS-CoV-2 might access CNS through a transsynaptic route and could thus cause respiratory failure in COVID-19 (Li et al. 2020c). Further the presence of ACE-2 receptors the membrane of spinal cord neurons suggests that SARS-CoV-2 can enter the spinal cord and thus cause ATM or other neurological effects (Valiuddin et al. 2020). These reports indicate that COVID-19 has a potential to produce complex neurological effects post SARS-CoV-2 infection and should be kept in mind while examining a COVID-19 patient (Mao et al. 2020a).

## Demyelination/ADEM

Several case reports from all around the world suggests an association between the spectrum of Guillain–Barré syndrome (GBS) and COVID-19 (Alberti et al. 2020; Zhao et al. 2020b). GBS is an immune-mediated acute-onset demyelinating polyradiculoneuropathy (acute inflammatory demyelinating polyneuropathy—AIDP) typically presenting with ascending weakness, loss of deep tendon reflexes and sensory deficits (Leonhard et al. 2019). Abu-Rumeileh S et al. reviewed that 73 SARS-CoV-2 patients suffered from

GBS and other associated forms of acute inflammatory demyelinating polyneuropathy (Abu-Rumeileh et al. 2020). A study from Singapore showed that COVID-19 patients exhibited varying certainty of relationship with acute disseminated encephalomyelitis (ADEM) and encephalitis (Koh et al. 2020). Case reports regarding COVID-19 associated demyelinating complications of the CNS are limited with few reports of acute disseminated encephalomyelitis (ADEM) and meningo-encephalitis in a severe COVID-19 patient being published to date (Moriguchi et al. 2020; Parsons et al. 2020; Reichard et al. 2020; Zanin et al. 2020). Palao M et al. reported the first presentation of demyelinating disease in the form of optic neuritis following COVID-19 infection (Palao et al. 2020). Viral infections are known to be associated with development of demyelinating diseases (Donati 2020), which fuels the hypothesis of SARS-CoV-2 induced demyelination. The delayed CNS damage appears mediated by the immune system (Klein et al. 2017). The cytokine storm (IL1, IL-6, and TNF- $\alpha$ ) post SARS-CoV-2 infection could be responsible for glial cells activation and subsequent demyelination (Mehta et al. 2020). These reports suggest that acute neurological complications in COVID-19 patients may be sustained by demyelinating lesions, and therefore early CSF analysis and prompt invasive treatment should be adopted to avoid CNS injuries.

## Hypoxia

Respiratory dysfunction in the COVID-19 patients leads to a decreased level of oxygen and followed by hypoxia (Cavazzi et al. 2020). Normal blood oxygen levels are around 95% and the brain may not get sufficient oxygen if this level falls below 90% (Berim 2020). The brain being the most sensitive organ to oxygen, a reduced alveolar gas exchange would directly affect its physiology and could initiate an irreversible set of pathological complications (Berim 2020). Also, an increase in the anaerobic metabolism in the mitochondria of the brain cells, could lead to a higher level of lactic acid, lipid peroxides, oxygen-free radicals and weakened antioxidant system, and BBB disruption which could contribute to CNS complications (Bhattacharyya et al. 2014). Interestingly, an increase in the level of lactic acid results in a decreased pH which is hypothesized to favour SARS-CoV's survival and growth (Li et al. 2020b, 2020c). Hypoxia can also lead to various complications such as increased intracranial blood flow, cerebral capillary pressure, dilation of intracranial blood vessels, tissue fluid production, brain free radicals, and membrane lipid peroxidation (Berim 2020; Cipolla 2009). Hypoxia further

causes metabolic acidosis which surges cerebral vasospasm and permeability, leading to interstitial brain edema, hypertension in the intracranial region, and reduced ATP production (Berim 2020; Cipolla 2009; Sekhon et al. 2017). This initiates the intracellular  $\text{Ca}^{2+}$  overload, oxidative stress, neurocognitive deficits, and brain injury (Sekhon et al. 2017). Extended hypoxia in COVID-19 patients could induce or attenuate several cerebrovascular events such as acute ischemic stroke, increased blood viscosity, and increased haematocrit levels (Desforges et al. 2020).

## Conclusion

The outreach and impact of COVID-19 has not been limited to respiratory tract, and the myth that this virus' interference normal respiratory physiology only has been confidently challenged. COVID-19 by altering BBB permeability and through neuronal transport, haematogenous route and through attachment to ACE-2 receptor gains access to CNS and thus has the ability to impact neuronal dynamics. Plethora of evidence suggests that COVID-19 induced neuronal damage involves provocation of inflammatory pathways and inducing a cytokine storm syndrome. The involvement of cytokines is well documented in majority of neurodegenerative pathologies (Alzheimer's disease, Huntington's disease and Parkinson's disease) and neuropsychiatric complications (depression and anxiety) etc. thus probability of these complications also multiplies with COVID-19. This apprehension gets strength through clinical findings of COVID-19 patients which reports emergence of complications like Parkinsonism, Alzheimer's disorder, epilepsy, intracranial infections, encephalitis, meningitis, dizziness, depression, anxiety, confusion, headache, insomnia, stroke, myelitis etc. in these patients. These findings suggest that COVID-19 cannot just be considered as a disorder of the pulmonary or peripheral system rather it has complex web of associated pathologies. Although, these accumulated evidences are yet at preliminary stage which further necessitates proper validation and confirmation yet these findings suggest that the CNS aspects of COVID-19 should be monitored very closely to prevent long term complications, even after the patient has recovered from COVID-19.

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