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# Neurological Involvement in COVID-19

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## Abstract

The respiratory system is the most common target of COVID-19, however, various experimental studies and case reports have shown its affinity for neural tissues. In this chapter, we described pathogenesis and propagation of SARS-CoV-2 virus in the nervous system, potential routes of the SARS-CoV-2 invasion in the brain, as well as indirect effects of COVID-19 on multiorgan disorders. We have also presented all of the reported neurological manifestations in COVID-19 with an explanation of possible underlying pathways. Among patients who tested positive on SARS-CoV-2, various neurological irregularities have been described, affecting both the central and peripheral nervous systems. In general, neurological complications in COVID-19 patients occur within 1 and 14 days, in most cases on average on the 5th day of the incubation period. We have demonstrated all of the reported neurological findings, whereas the most commonly reported were headache, dizziness, myalgia, hypogeusia, hyposmia, and impaired consciousness. More serious neurological conditions in COVID-19 included meningitis, encephalitis, and ischemic or hemorrhagic stroke.

**Keywords:** SARS-CoV-2, neurologic manifestations, pathogenesis, COVID-19, coronavirus

## 1. Introduction

The infection of coronavirus (SARS-CoV-2) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. Regarding its structure and infection mechanism, SARS-CoV-2 is mostly similar to familiar coronaviruses such as the SARS-CoV-1 and Middle East respiratory syndrome (MERS) [2, 3]. Identified in Wuhan, China, it has abruptly spread all over the world with more than 164.513.450 reported cases to date [4]. The respiratory system is the most common target of infection however, various experimental studies and case reports have shown an affinity for neural tissues. Considering observational studies, SARS-CoV-2 patients were registered with complaints of headache, nausea, vomiting, dizziness, myalgia, hypogeusia, hyposmia, and impaired consciousness, all symptoms that indicate involvement of the nervous system [5]. Even though, the exact mechanism which SARS-CoV-2 penetrates the central nervous system has not yet been determined, prior experimental models have

shown that other coronaviruses can compromise the nervous system and respiratory drive by directly targeting neurons located in cardiorespiratory centers [6], due to the preliminary observation of cases concerning the COVID-19 pandemic, suggesting a higher affinity of SARS-CoV-2 virus for CNS targets.

The aim of this chapter is to present all of the reported neurological manifestations in COVID-19 with the explanation of possible underlying pathways.

## **2. COVID-19 and nervous system**

In the previous months, reports of meningitis, encephalitis, myelitis, or peripheral nerve affection in regard to COVID-19 infection were presented, implying that SARS-CoV-2 can directly infect the nervous system.

### **2.1 Pathogenesis**

The SARS-CoV-2 spike protein (S) can bind to the host cellular angiotensin-converting enzyme 2 (ACE-2) receptor because of its high binding affinity, which is of importance to cell tropism [7]. Preparing and processing of the S protein by the transmembrane protease serine 2 (TMPRSS2) have been demonstrated to be crucial for the synthesis of viral and host cellular membranes, furthermore entrance of SARS-CoV-2 [8]. The increased expression of the ACE-2 receptor has been found on neurons and glial cells of several brain structures including the cerebral cortex, the striatum, the posterior hypothalamic area, the substantia nigra, and brain stem. ACE-2 is strongly expressed in the ventrolateral medulla and the nucleus of tractus solitarius, both areas involved in the regulation of the respiratory cycle [9].

Arguably, several mechanisms could be taken into account as possible viral access routes, such as axonal transport and trans-synaptic transfer, and hematogenous or potentially lymphatic system routes. The infiltration of the CNS through the transcribrial system describes an infection of the olfactory epithelium continuing transmission through the cribriform plate to the subarachnoid space. On the other side, the axonal and trans-synaptic transport would combine numerous peripheral nerve terminals which leads to contamination by spreading onward neurons (olfactory bulb, the trigeminal nerve, the vagus nerve, etc.) [10].

Another way of CNS infiltration could be through the circulatory system or on the other hand, the lymphatic system routes. Transfer over the brain endothelium could be accomplished through abluminal virus release into the CNS parenchyma, by direct infection of brain microvascular endothelial cells (BMEC), or via endocytosis, through virally affected leukocytes or disrupted tight junctions on BMEC-s [11].

However, direct contamination of cells is not the only way of virus transmission. Indirect neurotoxicity may be caused by immune system disorders, coagulation disorders, cardiovascular comorbidities, disorders of glucose and lipid metabolism, hypoxic encephalopathy, and/or gastrointestinal disorders.

Other than ACE-2, SARS-CoV-2 may utilize extracellular matrix metalloproteinase inducer also known as basigin (BSG; CD147) and transmembrane glycoprotein neuropilin-1 (NRP1) as receptors. Some enzymes that catalyze proteolysis such as TMPRSS11A/B, cathepsin B and L, and furin (FURIN), have been presented to promote viral cell entry and replication [12].

### **2.2 Propagation of SARS-CoV-2 virus in the nervous system**

Dissemination of SARS-CoV-2, in which the virus has an effect on peripheral neurons via active transport, synaptic terminals, and retrograde transport to the

neuronal body of the cell, has been hypothesized [13]. Studies have been conducted, explaining the mechanism of trans-synaptic transfer involving the hemagglutinating encephalomyelitis virus strain 67 N (HEV-67 N), which represents the first SARS-CoV-2 strain that was found to infect the porcine cerebrum [14]. Data from human single nuclei RNA-seq databases suggest that vascular endothelial cells may express ACE-2 in the human cerebrum at low levels, however non-canonical SARS-CoV-2 receptors (e.g., BSG/CD147) are displayed in several different brain cell types, making them exposed to the virus [15].

### 2.3 Potential routes of SARS-CoV-2 invasion in brain

Provided by other viruses of the family Coronaviridae, certain possible routes of entry for SARS-CoV-2 have been established [16].

#### 2.3.1 Olfactory route

The olfactory nerve (CN I) is the first and shortest cranial nerve. It is a special visceral afferent nerve, which transmits information relating to smell. The sense of smell is distinguished by olfactory receptors situated within the nasal epithelium. Their axons amass into small bundles of olfactory nerves, which infiltrate small foramina in the cribriform plate of the ethmoid bone and enter the cranial cavity. The absence of the sense of smell is defined as anosmia. A temporary loss of smell can be caused by infection or by local disorders, in contrast, a permanent loss of smell may be caused by head injury or tumors. Infection of the olfactory system is consistent with the observation that loss of smell is a frequent neurological manifestation in COVID-19. Some evidence, demonstrate increased MRI signal in the olfactory cortex during the acute phase of SARS-CoV-2 infection [17]. As represented in the case of other coronaviruses, the virus could be disguised in nerve terminals by endocytic mechanisms, transported retrogradely, and spread trans-synaptically to other regions of the cerebrum [18]. As described before, ACE-2 and TMPRSS2 have been identified in the nasal mucosa, epithelial cells (sustentacular cells), but not olfactory neurons [19]. However, there are some evidences of neuronal involvement.

#### 2.3.2 Blood: brain route

The blood-brain barrier (BBB) acts as an additional boundary between circulating blood and the extracellular space of the brain. The barrier is highly selective, protecting the brain from toxins, pathogens and even circulating neurotransmitters (e.g. glutamate) that can be potentially damaging to neurons. The BBB is a typical route of entry of blood-borne viruses into the brain. In SARS-CoV-2 infection, dissemination of the virus into the blood has been reported, even though frequencies are extensively ranging (1–41%) [16]. Immunoreactivity of ACE-2 was described in brain vessels of a patient with multiple ischemic infarcts. However, the cellular localization was not resolved. Other receptors, such as NRP1 and BSG, could be another possibility of infection due to their more widely expression in the cerebral vasculature [20]. Nonetheless, SARS-CoV-2 associated cytokines – interleukins (IL-6, IL-1b, IL-17) and tumor necrosis factor (TNF) can potentially damage the BBB, which is another way of virus invasion [21]. In several autopsy studies, a lack of florid cerebrovascular inflammation has been described [22]. Comorbidities, as have oftentimes been seen in COVID-19, such as cardiovascular risk factor or pre-existing neurological diseases, in combinations with activation of cytokines, increase the permeability of BBB [21].

### *2.3.3 Infiltration of infected immune cells*

Infected immune cells (monocytes, neutrophils, and T cells) can cause brain infestation through the vasculature, the meninges, and choroid plexus [16]. In a study conducted by Chen et al., 2020, SARS-CoV-2 nucleocapsid protein (NP) immunoreactivity was observed in CD68+ cells in lymphoid organs, while single-cell RNA seq data showed viral RNA in macrophages of COVID-19 patients [23]. However, data about virus proliferation in macrophages are limited due to the unknown mechanisms of virus propagation (phagocytic uptake of virus-infected cells or extracellular virions) [24].

## **3. COVID-19 and nervous system: indirect effects of systemic factors**

Indirect effects of systemic factors of SARS-CoV-2 can lead to acute and chronic consequences, such as respiratory failure, systemic inflammation, hypercoagulable state and, lethal systemic organ failure.

### **3.1 Respiratory failure**

SARS-CoV-2 has been predominantly detected in pneumocytes and epithelial progenitors, which can lead to potential lung damage, causing massive alveolar damage, inflammatory cell infiltration, edema, microvascular thrombosis, and hemorrhage resulting in severe hypoxia and acute respiratory distress syndrome (ARDS) [25, 26]. The most sensitive brain regions to hypoxia, such as the neocortex, hippocampus, and cerebellum have shown neuronal impairment [27].

### **3.2 Systemic inflammation**

The correlation between immunosuppression and disease severity has been established. Most COVID-19 patients have higher circulating levels of IL-6, IL-1b, and TNF, but also additionally IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, and MIP1a2, and serum levels of IL-6 and TNF leading to cytokine release syndrome [28–30]. After brain entry through the damaged BBB, certain molecules such as the nuclear protein high mobility group box 1 (HMGB1), could act as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [31]. This process activates an immune response in pericytes, brain macrophages, and microglia, which express toll-like receptors (TLR) which act as mediators for pro-inflammatory effects of SARS-CoV-2 spike protein on human macrophages through nuclear factor- $\kappa$ B (NF- $\kappa$ B) [32]. In this way, immune response boosts the level of cytokine production which results in impairment of brain function [33].

### **3.3 Hypercoagulable state**

Another vital element of COVID-19 is significant coagulopathy. The multicenter study has been conducted, suggesting that 88% of patients displayed evidence of a hypercoagulable state. The prothrombin time (PT), activated partial thromboplastin time (aPTT), and complete blood count (CBC) are in the reference range. However, fibrinogen level, and fibrin breakdown products indicative of intravascular thrombosis (D-dimer), are both increased. Coagulopathy may start in the lungs causing endothelial damage, complement activation, activation of the procoagulant



effect of IL-6, and neutrophil release of extracellular traps (NETs) that leads to the formation of a clot, resulting in intravascular thrombosis [34].

### **3.4 Systemic organ failure**

There are many metabolic and pathological evidence of systematic impairment in different organs (heart, liver, gastrointestinal tract, and endocrine system) [35]. Hypoperfusion of the cerebrum could be impacted by a compromised function of the heart [36]. Many neurological symptoms, for instance, headache, confusion, agitation, can be correlated to systemic metabolic changes including electrolyte disbalance, hormonal dysfunction and accumulation of toxic metabolites [37, 38].

## **4. COVID-19 and nervous system: neurological manifestations**

Although, SARS-CoV-2 is primarily causing the insufficient function of the respiratory system, there are overwhelming amounts of evidence implying that neurological complications appear as a serious problem in the ongoing COVID-19 pandemic. In the long-term, COVID-19 could negatively affect the nervous system [39].

Among patients who tested positive on SARS-CoV-2, various neurological irregularities have been described, affecting both the central and peripheral nervous system. Clinical condition and symptoms may vary from mild to severe, regardless of patient clinical status (severe form or asymptomatic infection). According to Helms et al., neurological abnormalities have been displayed in 30% of hospitalized patients, 45% of those with severe respiratory problems, and 85% of those who developed ARDS [40]. Patients with mild or asymptomatic infection were more likely to develop nonspecific neurological irregularity including headache, dizziness, malaise, and loss of sense of smell and taste.

In the review by Leonardi M, Padovani A, McArthur JC (2020) [41], authors have classified the reported neurological findings, into three distinctive categories:

- a. Central (headache, dizziness, impaired consciousness, acute cerebrovascular disease, seizures, and meningitis/encephalitis)
- b. Peripheral (hypogeusia, hyposmia)
- c. Musculoskeletal (ischemic or hemorrhagic stroke)

In general, neurological complications in COVID-19 patients occur within 1 and 14 days, in most cases on average on the 5th day of the incubation period [42].

### **4.1 Headache and dizziness: central neurological findings**

Headache is one of the most commonly reported neurological symptoms of a systemic viral infection. Although direct mechanisms of this symptom are yet to be discovered, there are some possible causes. High body temperature directly causes activation of several immunoinflammatory mediators (cytokines, glutamate, cyclooxygenase-2/prostaglandin E2 system, and nitric oxide system) and activation of substances that are capable of inducing interleukins (exogenous and endogenous pyrogens). Some of the indirect causes are dehydration, electrolyte disbalance, hypoxia, systemic inflammation, and cytokine release syndrome (CRS).

One of the possibilities for developing this symptom could also be direct infection of the nervous system via ACE-2 receptors [43].

Vertigo or dizziness has been described as the most common neurological manifestation of COVID-19. Neurotropism of SARS-CoV-2 causes the virus to invade neural tissue from circulation through capillary endothelium (ACE-2 receptors). Aside from this mechanism, direct invasion, hypoxia, and systemic inflammation play the part in causing this symptom. Approximately 7.0% (2.5% to 21.4%) of the COVID-19 patients were reported to have this symptom.

Combined manifestation of dizziness and headache occurred in 12.1% as has been reported in eight studies, with a total of  $n=654$  patients [44].

#### **4.2 Impaired consciousness: central neurological findings**

As anticipated, severe or critical patients tend to develop impaired consciousness (11.9%) due to hypoxia and cerebrum impairment. In patients with mild or asymptomatic clinical manifestations, the prevalence of this symptom is considerably lower (3.2%). The number of studies taken into account was nine, including  $n=2890$  patients with impaired consciousness [45].

#### **4.3 Acute cerebrovascular complications: central neurological findings**

The most common display of cerebrovascular disease is an acute stroke with rapidly evolving symptoms which may include weakness of one side of the face or body, numbness, motor or sensory aphasia, ataxia, visual impairment. Those symptoms could be manifested due to compromised blood supply to the brain and which symptom will develop depends on the compromised area of the cerebrum. Regarding this clinical problem, two cohort studies were conducted. The first study by Mao et al. noted that among 214 hospitalized patients, 6 patients developed acute cerebrovascular manifestation (2.8%) [46]. The second study by Li et al. reported 11 patients with acute ischemic stroke (including a total of 221 COVID-19 patients). It has been shown that developing acute cerebrovascular events is highly correlated with the age of the patients ( $71.6 \pm 15.7$  years/ $52.1 \pm 15.3$  years) [47].

#### **4.4 Seizures: central neurological findings**

An epileptic seizure is a “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” [48]. There are few reports of acute seizures in SARS-CoV-2 positive patients. The first study regarding this clinical manifestation was noted in a COVID-19 patient, a 24-year-old male with generalized seizures, from Japan [49]. The second publication reported a COVID-19 patient, a 30-year-old female with generalized tonic-clonic seizures, from Iran. In both cases, there was no evidence of previous seizures, prior to hospitalization [50]. Even though these and similar reports may suggest that correlation between seizures and COVID-19 infection exist, there are a relatively low number of reported cases so far, therefore a seizure risk is caused by nonspecific mechanisms (hypoxia, cerebrovascular events, cytokine proliferation, etc.).

#### **4.5 Meningitis/encephalitis: central neurological findings**

By definition, meningitis is inflammation of the meninges, in almost all cases identified by an abnormal number of leukocytes in the cerebrospinal fluid and specific symptoms. The etiology may be noninfectious and associated with a systemic disease, medication, or other pathologic factors. However, most cases of

aseptic meningitis are caused by viruses. There have been interpreted few single-case reports, regarding meningitis/encephalitis in correlation with COVID-19. Anyhow, only a few of reported cases tested positive for SARS-CoV-2. The first described case was reported from China, but the amount of clinical evidence was underwhelming [51]. Another case was reported in a SARS-CoV-2 positive patient from Japan, manifested as generalized seizure and pathological cerebral MRI (right lateral ventriculitis and encephalitis mainly on the right mesial temporal lobe and hippocampus) [52]. In other reported cases, patients tested negative for SARS-CoV-2, or even were not tested at all [53].

#### **4.6 Hypogeusia/hyposmia: peripheral neurological findings**

The presence of taste and smell alterations seems to be a usual clinical manifestation going from 19.4–88% of patients [54]. The specific pathogenesis of these issues has not yet been explained. ACE-2 has been distinguished as the cell receptor for SARS-CoV-2. These receptors are expressed diffusely on the mucous membrane of the entire oral cavity, especially on the tongue and furthermore on the nasal mucosa where it takes part in respiratory inflammatory infections by regulating the level of inflammatory peptides, for example, bradykinin. There have been many reports regarding alteration of the senses of smell and taste. The one particular larger study, including a total of 417 patients with mild to moderate SARS-CoV-2 infection, described smell impairment in 85.6% and taste impairment in 88.8% [55].

#### **4.7 Stroke: musculoskeletal neurological findings**

Stroke is commonly defined as sudden neurological deficit as a result of infarction or hemorrhage in the central nervous system [56]. This is a traditional definition, which has been updated over time with the fact that the neurological symptoms need to last more than 24 hours or CT and MRI confirmed focal infarction or hemorrhage compatible with the symptoms [57]. The typical subdivision of stroke includes ischemic stroke (infarction of brain, retina, or spinal infarction) and hemorrhagic stroke (intracerebral or subarachnoid hemorrhage) [58]. The cause of ischemic stroke is thromboembolism from the small vessel, larger artery, or the heart [59]. Classification of the hemorrhagic stroke depends on the anatomical location, whereas the most common are supratentorial hemorrhages [60].

There are numerous studies that report acute stroke complicating COVID-19 [61, 62]. The reported incidence of acute stroke in COVID-19 varies from 0.4% to 8.1%, due to the different ethnic and geographical variations: Asia (3.1%), Europe (1.2%) and, North America (1.1%) [63]. The reported incidence of stroke in COVID-19 patients treated in the intensive care units (ICU) is 1–3% [64–68]. Given the extent of the COVID-19 pandemic, this reported incidence is very high. Hemorrhagic stroke has been described from 21.7% to 25.7% COVID-19 patients with stroke, while the rest were ischemic strokes [69].

It has been stated that male COVID-19 patients, the median age of 63 years, are more likely to experience a stroke than women, but it is also known that the majority of ICU COVID-19 patients are older men as well [67]. Other reported risk factors include hypertension, diabetes mellitus [66, 70]. Race/ethnicity is also an important risk factor and it was observed that the black race had shown the highest prevalence (47%) [71]. A severe type of COVID-19 infection was observed as one of the most important risk factors for stroke in these patients [72–76]. There is a causal relationship between COVID-19 and stroke since the infection itself is more likely to induce thrombotic vascular events [63].



Described mechanisms of stroke in COVID-19 patients are diverse and multifactorial, considering that COVID-19 could be a trigger to typical stroke mechanisms, or alternatively, there are specific pathophysiological mechanisms [63]. The mechanisms for ischemic stroke in COVID-19 include sepsis-induced coagulopathy, presence of antiphospholipid antibodies, and thromboembolism, which show activated coagulation pathway in patients with COVID-19 who ordinarily already have elevated D-dimer and fibrinogen [77–81]. It is well known that COVID-19 uses the ACE-2 receptor to enter the cells, which leads to increased sympathetic activity, loss of blood pressure auto-regulation, and subsequent cerebral hypoperfusion [82]. Cytokine storm has also been suggested as one of the mechanisms in stroke development in COVID-19, due to its impact on atherosclerosis and thrombosis [83]. Finally, hypoxemia in COVID-19 patients may cause cerebral hypoperfusion and increase the risk of ischemia, together with previously explained thromboembolic mechanisms [84, 85].

Hemorrhagic strokes are less prevalent than ischemic strokes, but it has been implicated that some mechanism which plays a role in ischemic stroke, could lead to intracerebral hemorrhage in COVID-19 [86]. The proposed mechanisms include viral damage of vessel wall, downregulation of RAS and hypertension, cytokine destruction of blood–brain barrier, consumption coagulopathy caused by COVID-19 and cerebral hypoxia which induces micro-hemorrhages and microbleeds [87, 88]. It has been reported that COVID-19 patients who develop stroke are distinctly susceptible to large vessel occlusion, multi-territorial involvement and engagement of else ways infrequently affected vessels such as pericallosal artery [66, 68, 89].

Neuroimaging of stroke in COVID-19 patients standardly includes CT, MRI, and CT angiography (CTA). Small vessel occlusion in acute ischemic stroke was reported in 9% of cases, while large vessel infarctions were seen in almost 65% of cases [67, 68, 71, 90]. More frequent were ischemic strokes in posterior circulation [91]. It has been demonstrated that CTA verified occlusion in anterior or medial cerebral arteries with the co-development of floating thrombi in aorta and carotid arteries in patients with high D-dimer values, which confirms the influence of hypercoagulable state [71, 92]. Apart from standardly seen ischemic lesions, a small number of the patients (two of them were children) with acute stroke had: vasculitis or wall enhancement on MRI in the arterial wall [93]. Imaging findings of the hemorrhagic stroke include extensive hemispheric hematomas or multiple hematomas [94–97]. Hemorrhages may develop in severely ill patients, especially due to the failure of multiple organs or as a transformation of ischemic stroke, aneurysm rupture, or thrombosis of central venous sinus [66, 97, 98]. Some authors report a possible correlation between COVID-19 and arterial dissection, seen in the carotid artery, cervical vertebral artery or in posterior inferior cerebellar artery [99, 100].

A very small samples of patients were presented with acute stroke confirmed on neuroimaging and PCR confirmed COVID-19 [101]. Described atypical neuroimaging findings are seen in small number of COVID-19 patients with stroke and consist of: brain perfusion abnormalities, leptomenigeal enhancement [eight patients], focal cortico-pial enhancement in one patient, posterior reversible encephalopathy syndrome, microbleeds or leuco-encephalopathy [66, 102, 103]. Atypical findings express latent thrombotic angiopathy, vascular disruption and impairment of vascular auto-regulation of the brain which happens in COVID-19 patients with stroke [103, 104].

## **5. Conclusions**

Even though the COVID-19 virus is primarily a respiratory infection, new reported cases of neurological involvement have been presented daily all over the

world [105]. In this chapter, we portrayed the neurological manifestations and possible pathophysiological mechanisms of SARS-CoV-2 on nervous system [105]. Given the extent of the COVID-19 pandemic, it is important to monitor COVID-19 patients for potential neurological complications to provide them with timely diagnostics and treatment.

### Conflict of interest

The authors declare no conflict of interest.

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