Pathophysiological Mechanisms and Neurological Manifestations in COVID-19

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Abstract

With increasing knowledge of the coronavirus disease 2019 (COVID-19), we now understand that COVID-19 presents with various extrapulmonary manifestations with multiorgan involvement. Involvement of the central nervous system (CNS) occurs probably via transsynaptic spread or transfer across the blood–brain barrier. Hypoxia, immune-mediated injury, and vascular damage are the potential mechanisms for the CNS manifestations. Headache, dizziness, chemosensory disturbances, such as loss of smell, taste, encephalopathy, stroke, etc., are among the commonly encountered neurological presentations. Headache is identified as one of the red flag symptoms for COVID-19. Sudden onset of loss of smell and/or taste in the absence of nasal congestion can help in COVID-19 case identification and testing prioritization. Both hemorrhagic and ischemic brain injury is common in patients developing stroke. Besides these, COVID-19-associated CNS involvement demands more careful attention toward patients with existing neurological disorders especially that are managed with immunosuppressant agents. In all, neurological involvement in COVID-19 is not uncommon and may precede, occur concomitantly or after the respiratory involvement. It may also be the sole presentation in some of the patients necessitating high vigilance for COVID-19. In this review, we briefly discussed the pathogenesis of CNS involvement and some important neurological manifestations in COVID-19.

Keywords: Anosmia, Central nervous system, Coronavirus disease 2019, Encephalopathy, Headache, Stroke.

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Introduction

Coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus has affected over 12 million people and caused over half a million deaths globally.[1] Coronavirus disease 2019 clinical syndrome can manifest with varying clinical features. A large number of patients with COVID-19 may remain asymptomatic, but many symptomatic patients have features like fever, dry cough, sore throat, dyspnea, fatigue, and myalgia. Though pulmonary involvement is typical, non-pulmonary, or atypical presentations are not uncommon.[2] Coronavirus disease 2019 can present with neurological involvement with symptoms, such as headache, giddiness, and dizziness, and some may develop encephalopathy and stroke.[2,3] Some of the neurological manifestations may be related to hypoxia or metabolic acidosis but the novel coronavirus has also been detected in the cerebrospinal fluid (CSF).[2] The exact pathogenesis of neurological involvement remains unclear, but possible theories include thrombi formation in the brain vessels and binding of the virus to the angiotensin-converting enzyme 2 (ACE-2) receptors in the central nervous system (CNS).[4,5] During this COVID-19 pandemic, intensivists must understand that patients may present with non-specific neurological symptoms that should not be ignored. Higher levels of vigilance are thus necessary for extrapulmonary and atypical symptoms, to prevent late diagnosis and to curtail the risk of COVID-19 transmission. In this review, we discuss the pathophysiology and neurological manifestations of COVID-19.

Pathophysiology of CNS Involvement

It is now known that the presence of ACE-2 receptors is essential for cellular entry of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The spike proteins on the viral surface bind to the ACE-2 receptor on the host cells and enter the cells.[4]

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The ACE-2 presence on the tissues determines viral cellular tropism. In humans, multiple tissues express the ACE-2 receptors including the epithelium of the airway, lung parenchyma, renal cells, small intestine, vascular endothelium, and the CNS.[6]

Neuroinvasion Mechanisms

Multiple mechanisms may underlie CNS involvement in SARS-CoV-2 infection, such as transfer across synapses from the infected neurons, entry via the olfactory nerve, transfer via vascular endothelium, or white cells traversing the blood–brain barrier (BBB).

Transsynaptic Spread

Transfer across the synapses has been documented for various coronaviruses (e.g., avian bronchitis virus, hemagglutinating encephalomyelitis virus 67, etc.).[7,8] Retrograde transsynaptic spread with either endocytosis or exocytosis and fast axonal transport of vesicles along the microtubules are suggested mechanisms for transfer of coronaviruses.[6] These mechanisms have also been postulated as possible route for CNS entry of SARS-CoV-2 after crossing cribriform plate of ethmoid bone. Loss of smell and taste are common in COVID-19, and the presence of these symptoms have a good predictive value in assessing household contacts of COVID-19 patients.[9,10] However, damage to the olfactory epithelium rather than to olfactory neuronal cells has been the suggested mechanism for loss of smell.[6]

Passage across BBB

Severe acute respiratory syndrome coronavirus-2 can invade CNS by passage across vascular endothelial cells (all endothelial cells express ACE-2) or by passage of virus infected leukocytes through the BBB, known as the Trojan horse mechanism.[6] As SARS-CoV-1 which infects cell types expressing ACE-2, such as lymphocytes, granulocytes, and monocytes, SARS-CoV-2 is also expected to infect these cells.[11–13] Increased permeability of BBB caused by systemic inflammation in the COVID-19 infection might allow passage of infected immune cells and thereby virus entry into the CNS.[14]

Pathophysiology of Neurological Damage

Multiple mechanisms of neurological injury are postulated and predominantly include hypoxic brain injury, immune-mediated damage, and cerebrovascular injury.

Hypoxia-induced Brain Injury

Pneumonia is characteristic in SARS-CoV-2 infection and in severe cases results in respiratory insufficiency and resultant hypoxia. Chronic persistent hypoxia can result in neurological injury. Hypoxia coupled with peripheral vasodilatation, anaerobic metabolism, and accumulation of toxic waste leads to neural swelling, cerebral edema, and progressive cerebral injury.[15,16]

Immune-medicated Brain Injury

Severe COVID-19 infection is characterized by cytokine storm with dysregulated release of excessive quantities of inflammatory cytokines [e.g., interleukin (IL) 6] along with the activation of immune cells, such as T cells, macrophages, and endothelial cells. The excessive cytokine release results in vascular leakage, activation of complement and coagulation cascade proceeding disseminated intravascular coagulation and ultimately multiorgan failure.[17]

Cerebrovascular Injury

Severe acute respiratory syndrome coronavirus-2 binding to the endothelial ACE-2 receptors may lead to increase in luminal pressure in the vessels, which may cause bleeding in the brain. In addition, abnormalities in coagulation system, such as thrombocytopenia, increased levels of D-dimer contribute to intracerebral bleeding especially in severely ill COVID-19 patients.[16]

Other Potential Mechanisms

Nerve cells lack major histocompatibility complex antigens, and therefore, viral elimination depends on the action of cytotoxic T cells. Neuronal apoptosis after virus infection may also exert a relatively protective effect. In addition, the homeostasis characteristics of the cells in the CNS assist in existence of the virus.[14]

Neurological Manifestations in COVID-19

Current evidence indicates that COVID-19 involves not only the CNS but also peripheral nervous system (PNS). Table 1 enlists the neurological manifestations that are discussed below.

CNS Manifestations

Headache

Though non-specific, headache is one of the predominant symptoms in COVID-19 and the reported incidence varies from 3% to up to one-third of patients.[6,16] In hospitalized patients, headache prevalence varies from 11 to 34%. Characteristically, headache in COVID-19 is moderate–severe bilateral headache with pulsating or pressing quality in the temporoparietal, forehead, or periorbital region. Headache may be gradual in onset or sudden and responds poorly to common analgesics. Relapse rate is high.[18] A Cochrane COVID-19 Diagnostic Test Accuracy Group identified headache along with symptoms of fever, arthralgia/myalgia, and fatigue as red flags for COVID-19 (positive likelihood ratio of ≥5).[19] However, the exact pathophysiology of headache is unclear. The suggested contributory mechanisms include direct viral invasion of the nervous system as well as the cytokine release syndrome. Release of the cytokines and chemokines stimulating the nociceptive sensory neurons may be the cause of the pain. Additionally, activation of peripheral trigeminal nerve endings also contributes to headache development.[18,20,21]

Table 1: Neurological manifestations in COVID-19

System involvement	*Neurological manifestations*
Central nervous system	Headache
	Dizziness
	Impaired consciousness
	Toxic–metabolic encephalopathy.
	Hypoxic encephalopathy.
	Acute hemorrhagic necrotizing encephalopathy.
	Encephalitis.
	Seizures
	Stroke
	Acute myelitis
Peripheral nervous system	Chemosensory disturbances
	Loss of smell.
	Loss of taste.
	Guillain–Barré syndrome
	Skeletal muscle damage

Dizziness

Dizziness is another non-specific symptom that may be evident in 10–14% patients with COVID-19.[22,23] In some reports, dizziness was reported in up to 20% cases.[24] A meta-analysis of 33 studies (7,559 participants) reported an identified dizziness prevalence of 8.7% (95% CI 5.02–13.43).[25]

Impaired Consciousness

A study from China reported impaired consciousness in 37% of hospitalized COVID-19 patients.[24] It could result from various causes, such as toxic–metabolic encephalopathy, seizures, or from demyelinating disease. Additionally, direct CNS infection with parenchymal involvement may cause impaired consciousness.

Toxic-metabolic Encephalopathy

Hospitalized COVID-19 patients have various derangements, such as severe inflammation, cytokine storm, sepsis, and renal dysfunction. The cytokine storm in severe COVID-19 is associated with increased levels of ILs, such as IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor α.[26] Along with the accumulation of toxic metabolic products, increased levels of cytokines and other inflammatory markers contribute significantly to toxic–metabolic encephalopathy.

Hypoxic Encephalopathy

In patients with severe pneumonia, hypoxia is very common. In some cases, hypoxia may be severe and results in a confusional state. A retrospective case series from China reported hypoxic encephalopathy in 20% of patients.[27]

Acute Hemorrhagic Necrotizing Encephalopathy

Poyiadji et al., reported the first case of acute hemorrhagic necrotizing encephalopathy in a female airline worker in her late 50s. The characteristic features included symmetric, multifocal lesions with variable thalamic involvement.[28] A retrospective analysis assessed COVID-19 patients with new-onset of neurological involvement. Among 27 critically ill patients, 20 (74%) had encephalopathy, 2 (7%) had acute necrotizing encephalopathy, and 5 (19%) had vasculopathy.[29] Acute hemorrhagic necrotizing encephalopathy is a rare complication in viral diseases and a possible pathogenic mechanism is cytokine storm with BBB disruption and ultimate damage to the brain parenchyma.

Encephalitis

The first case of meningoencephalitis was reported in Japan.[30] Magnetic resonance imaging (MRI) of the brain showed hyperintensity along the wall of right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus. Importantly, nasopharyngeal swab for the specific SARS-CoV-2 RNA was negative but it was detected in the CSF.[30] Bodro et al., reported two cases with encephalitis associated with COVID-19. The first one was a 25-year-old man with headache, left-sided paresthesia, and ipsilateral paresis. Within 12 hours, symptoms progressed to confusion and agitation. In the second case, a 49-year-old man developed difficulty naming objects, temporospatial disorientation, confusion, and agitation within few hours of admission. In both cases, CSF was negative for SARS-CoV-2 but nasopharyngeal swab was positive. The increased levels of ILs in the CSF were demonstrated indicating encephalitis secondary to cytokine storm. Both patients recovered spontaneously.[31] Khoo et al., reported brainstem encephalitis secondary to SARS-CoV-2 infection in a 65-year-old woman who had widespread, stimulus-sensitive myoclonus involving the tongue and all four limbs, associated with hyperekplexia without habituation to tactile, visual, and auditory stimuli.[32] These cases indicate that encephalitis can be a presentation of COVID-19 and nearly eight cases of encephalitis have been identified.[33]

Seizures

Seizure as a presenting feature is rare in COVID-19. In a case report from Sohal and Mossammat, a 72-year-old man was diagnosed with COVID-19 and had comorbidities, such as hypertension, coronary artery disease with stent, type II diabetes, and end-stage kidney disease on hemodialysis. The patient developed multiple episodes of tonic–clonic movements of his upper and lower extremities on the third day of admission. Seizures responded to antiepileptic treatment.[34] From Spain, the analysis of the ALBACOVID Registry revealed a seizure prevalence of 0.7% among 841 hospitalized COVID-19 patients.[35] In a systematic review of 79 studies assessing neurological manifestations of COVID-19, Tsai et al., observed a seizure frequency of 1.5%.[36] A small study of 50 patients from Chicago reported seizures in 13 hospitalized cases.[37] Understanding about the pathomechanisms of seizures in COVID-19 is limited. Seizures may be a consequence of metabolic disturbances, hypoxia, cytokine storm leading to viral encephalitis, or viral invasion of mesial temporal lobe, especially in severe COVID-19 patients.[36]

Stroke

Severe inflammatory response and hyper-thrombotic state in COVID-19 increase the likelihood of stroke. Additionally, vascular endothelial infection and damage to the vessels also increase the risk of ischemic and hemorrhagic infarcts.[6] Extensive cerebral small-vessel ischemic lesions resembling cerebral vasculitis have also been identified in COVID-19 that increase the risk of stroke.[38] In their study from China, Mao et al., reported acute cerebrovascular disease in 5.7% of patients ($n = 5$), of which four patients had ischemic stroke and one had cerebral hemorrhage.[24] The ALBACOVID Registry from Spain observed cerebrovascular diseases in 1.7% patients.[35] A systematic review from Tsai et al., (79 studies) reported occurrence of acute cerebral vascular disease in 8.1%.[36] A report from Mahboob et al., suggests that new-onset large vessel stroke may occur in COVID-19. They reported new-onset dysarthria and hemiplegia in a 58-year-old COVID-19 positive woman. Magnetic resonance imaging revealed a left cerebellar infarction in the territory of the posterior inferior cerebellar artery (PICA). This new-onset ischemic stroke occurred despite consistent use of dual antiplatelet therapy (DAPT). This is a rare occurrence where patient presented solely with focal neurological deficits.[39] Multiple reports indicate both ischemic and hemorrhagic strokes can occur in severe COVID-19.

Stroke development is often associated with mortality. Though the number of males was higher than females, no differentiation by age (<50 or >50 years) was evident.[40–42] A report from an international panel provided opinions on management of acute ischemic stroke in patients with COVID-19. Intravenous thrombolysis and mechanical thrombectomy have been advised only in selected patients. The panel suggested that favorable outcomes are likely with mechanical thrombectomy in properly selected patients when initiated and performed rapidly.[43]

Acute Myelitis

Reports of acute necrotizing myelitis, acute transverse myelitis, and acute disseminated encephalomyelitis indicate wide variety in neurological involvement with SARS-CoV-2.[44–46] Treatment with steroids, immunomodulators, and plasma therapy proved beneficial in these cases.

PNS Manifestations

Chemosensory Disturbances

Loss of taste and smell are now established symptoms of COVID-19. While analyzing the data of 3,563 patients from 18 studies, Borsetto et al., reported that the overall prevalence of alteration of the sense of smell or taste was 47%. The prevalence rates varied between 31 and 67% in severe and mild-to-moderate symptomatic patients, respectively. The loss of smell and taste preceded other symptoms in 20% of cases and it was concomitant in 28%.[47] These sensory disturbances may be the only presenting symptoms in some patients. The pathogenesis of such chemosensory disturbances is yet to be fully understood, the hypotheses proposed is that SARS-CoV-2 might alter the cells and circuits involved in chemosensory processing and thereby change perception. This hypothesis along with other potential mechanisms of pathogenesis of change of smell and taste are extensively reviewed by Cooper and colleagues which readers can refer for further information.[48]

Currently, COVID-19 patients with mild disease are home-quarantined. In household contacts of such home-quarantined patients, Boscolo-Rizzo et al., reported loss of smell or taste in 22.3% contacts and 4.0% of contacts had loss of smell or taste in the absence of other symptoms.[9] Dawson et al., reported loss of taste and/or smell as the fourth most reported symptom (62%) among COVID-19 patients. Presence of these symptoms had the highest positive predictive value (83%; 95% CI 55–95%) among household contacts. Thus, the presence of sudden onset loss of taste and/or smell in people without nasal congestion should be considered for COVID-19 case identification and testing prioritization.[10]

Guillain–Barré Syndrome (GBS)

So far, 16 cases of GBS after COVID-19 have been published.[49] Guillain–Barré syndrome affects peripheral nerves and manifests as demyelinating neuropathy with ascending paresthesia and weakness. Though temporal association with occurrence of GBS was seen in many reports (duration of onset of symptoms varied from 5 to 10 days postinfection), the evidence of direct invasion of nerves or nerve roots is unclear.[50] In such cases where follow-up duration may be short, acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) should be considered among the differential diagnosis.[51] Treatment with immunoglobulins, plasma exchange may help in better recovery.[51,52]

Skeletal Muscle Damage

Mao et al., reported muscle injury in 19.3 and 4.8% of severe and non-severe category of COVID-19 patients, respectively.[24] Angiotensin-converting enzyme 2 receptors are also expressed on skeletal muscles, and invasion of skeletal muscles through ACE-2 receptors may play a key role in the pathogenesis of injury.[15] Additionally, increased lactate levels, low pH, and low oxygen levels add up to muscle pain. Such pain may not be responsive to analgesics and viral exclusion may relieve the pain.[53]

Consideration for COVID-19 Patients with Preexisting Neurological Disorders

Patients with preexisting neurological disorders may have a disease spectrum that may put them at a greater risk of acquiring COVID-19 infection. It should be noted that patients aged >65 years, comorbid lung disease, diabetes, renal disease on dialysis, or receiving immunosuppression are at risk of severe disease.[6] We discuss few important neurological disorders that may put patients at higher risk of COVID-19 infection, below.

Multiple Sclerosis (MS)

Patients with MS being treated with disease-modifying therapies that have immunosuppressive effects are at a risk of severe COVID-19 infection. However, continuation of disease-modifying therapies, such as steroids, is advised.[6] In patients at high risk of exposure to COVID-19, the MS International Federation recommends that before using additional immunosuppressive therapy (e.g., interferons, glatiramer acetate, or natalizumab), risks and benefits of such treatments should be considered. Interferons and glatiramer acetate are unlikely to impact negatively on COVID-19 severity.[54]

Neuromuscular Disorders

Among major neuromuscular disorders, patients with myasthenia gravis or Lambert–Eaton myasthenic syndrome who have respiratory muscle weakness are at risk of severe COVID-19. The International Myasthenia Gravis/COVID Working Group recommends continuing ongoing treatment. Social distancing and telemedicine visits are advised for patients receiving immunosuppressive therapy. As hydroxychloroquine exacerbates myasthenia symptoms, its use is contraindicated.[55]

Epilepsy

Patients with epilepsy are not at higher risk of infection and as none of the antiepileptic drugs have immunosuppressive properties they can be safely continued.[6] A survey of 100 epilepsy patients from Iran found that 31% of patients had hardship obtaining their drugs and 6% had worsening of their seizure control status in the past 4 weeks.[56] In treating patients of epilepsy with COVID-19, potential drug–drug interactions should be kept in mind considering the effects of inhibitors or inducers of cytochrome P450 system.[57]

CNS Effects of COVID-19 Therapies

Among the currently used treatments for COVID-19, hydroxychloroquine can cause irritability, psychosis, peripheral neuropathy, and neuromyopathy. It is contraindicated in myasthenia gravis patients. It interacts with antiepileptic drugs, such as lacosamide and lamotrigine. As it lowers seizure threshold, special consideration should be given in patients with existing epilepsy.[6] With tocilizumab, headache and dizziness are common. Rarely, multifocal cerebral thrombotic microangiopathy may occur.[58] Remdesivir is relatively free of neurological effects. A single case of delirium in a mechanically ventilated patients was reported in a remdesivir trial.[59]

Conclusion

Coronavirus disease 2019 is a multisystem disorder and SARS-CoV-2 has neurotropicity similar to other coronaviruses. Neurological involvement is common in COVID-19 and patients may present

with only neurological symptoms. Neurological manifestations may precede, occur concomitantly or after respiratory involvement. Prompt identification of symptoms with high index of suspicion especially in severe COVID-19 patients is necessary. Further research should focus on the short- and long-term CNS complications and their sequelae in patients of COVID-19.

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