

Neurological Problems in COVID-19 Pandemic

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Abstract

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This outbreak, which emerged in Wuhan city, rapidly spread throughout China and has now become a global public health concern. SARS-CoV-2 is a highly pathogenic and transmissible virus. Common clinical manifestations of COVID-19 include fever, dry cough, shortness of breath, muscle ache, headache, and confusion. Currently, there is no confirmed effective therapeutic strategy for COVID-19 because the pathological mechanism is poorly understood. In addition to the respiratory system involvement, recent evidence has shown that SARS-CoV-2 can affect other organ systems including nervous, vascular, digestive, and urinary system. Various neurological complications have also been described in various studies. Nervous system involvement in the case of SARS-CoV-2 is explained by direct neuro invasion, immune mechanism, and other systemic factors. Neurological complications due to SARS-CoV-2 include both central and peripheral nervous system involvement. Central nervous system complications range from mild headache to seizures, encephalitis, myelitis, and acute cerebrovascular accidents. Peripheral nervous system complications range from vague muscle pains to Guillain-Barré syndrome. This article briefly discusses the various neurological and mental health issues related to COVID-19.

Keywords

- neurological
- pandemic
- COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This outbreak, which emerged in Wuhan city, rapidly spread throughout China and has now become a global public health concern. As of May 21, 2020, globally 48,93,186 cases of COVID-19 have been reported, including 3,23,256 deaths.¹

The SARS-CoV-2 is from the family of large enveloped non-segmented positive-sense ribonucleic acid viruses.² SARS-CoV is a respiratory virus, which mutates quickly and causes common cold to severe diseases such as severe acute respiratory syndrome (SARS-CoV, 2002–2004) and Middle East

respiratory syndrome (MERS-CoV, 2013–2014). SARS-Cov-2 shares 88% genetic similarity with SARS-CoV and 50% resemblance with MERS-CoV.³

Clinical manifestations of COVID-19 are fever 83%, cough 82%, shortness of breath 31%, muscle ache 11%, confusion 9%, headache 8%, and sore throat 5%.⁴ SARS-CoV-2 is highly pathogenic and transmissible virus.⁵ Currently, there is no confirmed effective therapeutic strategy for COVID-19 because the pathological mechanism is poorly understood. In addition to the respiratory system involvement, recent evidence has shown that SARS-CoV-2 can affect other organ systems including nervous, vascular, digestive, urinary, and hematological.^{4,6} The pathological findings established the nature of multiorgan

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damage by SARS-CoV-2, which consists of pulmonary lesion and cerebral edema, microvascular steatosis, and thrombosis.⁷ Various neurological complications were also described in various studies from different regions of the world.

Neuropathogenesis: Nervous system involvement in case of SARS-CoV-2 is explained by direct neuroinvasion, immune mechanism, and other systemic factors (hypoxia, thrombosis, metabolic derangements).

Direct Neuroinvasion

Nervous System Route

SARS-CoV-2 is in the same beta-coronavirus clade as MERS-CoV and SARS-CoV, and shares highly homologous sequence with SARS-CoV that has been revealed in the genomic analysis.⁸ The evidence shows that COVID-19 shares similar pathogenesis and receptors for the entry of SARS-CoV-2 into human host cells as SARS-CoV.⁹⁻¹¹ Most CoVs share a similar viral structure and infection pathway and thus the infection mechanisms earlier found for other CoVs may also be applicable for SARS-CoV-2.^{12,13}

The animal and human experimental studies confirmed that either SARS-CoV or MERS-CoV was capable to infect the brain.¹⁴ Additionally, in one report the SARS-CoV was detected in the cerebrospinal fluid (CSF) of a patient with neurological consequence following SARS infection.¹⁵ The evidence of angiotensin-converting enzyme 2 (ACE2) expression by the glial cells and neurons in the brain further suggests neurotropism of the SARS-CoV-2.¹⁶⁻²⁰

The main transmission of CoV is through droplet spread; CoV-laden droplets sticking to the nasal mucosa travel to the lungs and also possibly enter central nervous system (CNS) through the olfactory nerve endings.⁵ This hypothesis of CNS invasion through the olfactory nerve endings could also explain the symptom of hyposmia in infected patients.^{21,22}

Hypogeusia triggered by SARS-COV-2 infection could result from injury to any of the three cranial nerves—facial, glossopharyngeal nerve, and vagus nerve, which carry the sense of taste to the nucleus of the solitary tract or thalamic nuclei.⁵ There lies a possibility of SARS-CoV-2 reaching the respiratory center from nucleus of the solitary tract due to close proximity, thus causing neurogenic refractory dyspnea.^{20,23}

Hematogenous Route

SARS-CoV-2 fixes to the ACE2 receptor on the alveolar epithelial cells, triggering endothelial damage and entering the blood circulation.⁵ The virus not only infects the epithelial cells but also the resident, infiltrating and circulating immune cells that secrete cytokines and these infected circulating immune cells transport the virus to other organs and may intensify the permeability of the blood-brain barrier, thereby encouraging the virus to enter the brain and causing viral encephalitis.²⁴ Although there is rare evidence that CoV, especially SARS CoV-2, invades the nervous system via the blood circulation pathway, subsequent studies are expected.^{25,26}

Digestive Tract Route

ACE2 receptors are expressed in intestinal epithelial cells also besides alveolar epithelial cells.⁵ The intestinal viral infection causes inflammatory reaction damaging the mucosal barrier, gaining entry into the blood circulation.^{5,27} There is a possibility of retrograde viral entry into the CNS through enteric nervous system.⁵

Lymphatics and/or Cerebrospinal Fluid Route

The virus may gain entry into the CNS through lymphatic pathway. It is capable of invading the hilar and mesenteric lymph nodes directly, ultimately entering the blood stream and thus spreading to the CNS.^{28,29}

Immune Mechanism

SARS and COVID-19 have led to a large number of mortalities, most of which have been due to multiple organ failure triggered by virus induced systemic inflammatory response syndrome.^{30,31} The ability of the virus to infect macrophages, microglia, and astrocytes in the CNS is principally important. Interleukin-6 has been correlated with the severity of COVID-19 symptoms.³²

Miscellaneous

The virus causes diffuse alveolar and interstitial inflammatory reaction in the lungs causing poor alveolar gas exchange. This in turn may lead to hypoxic damage in the central nervous tissue.^{33,34}

SARS-CoV-2 infection is associated with a prothrombotic state producing venous and arterial thromboembolism and elevated D-dimer levels.³⁵ Severe COVID-19 is linked with proinflammatory cytokines that induce endothelial and mononuclear cell activation with expression of tissue factor, leading to coagulation activation and thrombin generation and thrombotic tendencies causing ischemic and thrombotic episodes. It has been proposed that COVID-19 might stimulate the production of antiphospholipid antibodies as a mechanism of ischemic stroke.³⁶

The biological characteristics of the CNS may enable exacerbation of the neurological damage caused by CoV infections. The CNS has a dense parenchymal structure and the typical absence of permeability of its blood vessels is a barrier to virus invasion. Nevertheless, if a virus gains access to the CNS, it is hard to eliminate.³⁷ Due to the absence of major histocompatibility complex antigens in nerve cells, the removal of viruses in nerve cells depends exclusively on the role of cytotoxic T cells.³⁸

Neurological Manifestations

SARS-CoV-2 is mainly respiratory virus but various neurological manifestations and complications have been described in literature. Although there are plenty of studies and articles available on clinical features of COVID-19, dedicated studies on neurological manifestations are scarce. Available literature is summarized in ► **Table 1**.

Mao et al studied 214 patients of COVID-19 from China and of these, 78 (36.4%) had various neurologic manifestations. Seventy-eight patients (36.4%) had nervous system

manifestations: CNS (53 [24.8%]), peripheral nervous system (PNS) (19 [8.9%]), and skeletal muscle injury (23 [10.7%]). In CNS manifestations, the most common symptoms were dizziness (36 [16.8%]) and headache (28 [13.1%]). In patients with PNS involvement, the common symptoms were taste impairment (12 [5.6%]) and smell impairment (11 [5.1%]).³⁹

The patients with severe infection were relatively older (58.2 vs. 48.9 years) and had underlying disorders particularly hypertension (36.4 vs. 15.1%), and lack of typical clinical symptoms such as fever (45.5 vs. 73%) and dry cough (34.1 vs. 61.1%).³⁹

Furthermore, nervous system manifestations were significantly more common in severe infections compared with nonsevere infections (45.5 vs 30.2%).³⁹

Helms et al described the neurologic features in an observational series of 58 of 64 consecutive patients admitted to intensive care unit (ICU) due to acute respiratory distress syndrome following SARS-CoV-2 infection. Neurological complications were seen in 49/58 (84%) patients. As evaluated by confusion assessment method for ICU scale, agitation was the most common symptom 40/58 (69%) followed by confusion 26/40 (65%). Diffuse corticospinal tract signs with exaggerated tendon reflexes and bilateral extensor plantar reflexes were seen in 39 patients (67%). Of the patients who had been discharged, 15 of 45 (33%) had dysexecutive syndrome consisting of inattention, disorientation, or poorly organized movements in response to command. Two asymptomatic patients each had a small acute

ischemic stroke and one patient had a subacute ischemic stroke.⁴⁰

Li et al studied 221 consecutive hospitalized patients with COVID-19 infection. They found that 11 (5%) patients developed acute ischemic stroke, one (0.5%) developed cerebral venous sinus thrombosis, and one (0.5%) developed intracerebral hemorrhage. The mean age of patients who developed stroke (72 years) was higher (52 years). Of the 11 patients with ischemic stroke, five were associated with large artery disease, three with small artery disease, and other three with cardioembolic events. The fibrin D-dimer levels were 12-fold higher in patients who developed stroke demonstrating a hypercoagulable state.⁴¹

Yang et al did a retrospective, observational study and enrolled 52 critically ill adult patients with SARS-CoV-2 pneumonia who were admitted to the ICU in Wuhan, China, and found headache in 6% of the patients.⁴²

Central Nervous System

Cerebrovascular Accidents

Mao et al described six cases of cerebrovascular accident (CVA) in their cohort of 214 patients. There were five cases of ischemic and one case of hemorrhagic stroke.³⁹ The French cohort had three cases of ischemic strokes that were detected on neuroimaging when the patients undertook imaging for encephalopathy.⁴⁰ In a study by Li et al., the incidence of

Table 1 Neurological manifestations in COVID-19 as described in various studies

S.N.	Authors/year	Study population	Neurological manifestations	
1.	Mao et al ³⁹ (2020)	214 admitted patients (China)	CNS involvement (24.8%)	Dizziness: 16.8% Headache: 13.1% Impaired consciousness: 7.5% Acute CVA: 2.8% Ataxia: 0.5%
				Seizure: 0.5%
			PNS involvement (8.9%)	Taste impairment: 5.6% Smell impairment: 5.1% Vision impairment: 1.4% Nerve pain: 2.3%
			Skeletal muscular manifestations (10.7%)	Muscle pain
2	Helms et al ⁴⁰ (2020)	Case series of 58 patients (France)	Agitation in 69%, confusion in 65%, corticospinal tract signs in 67%, dysexecutive syndrome in 36%	
3	Li et al ⁴¹ (2020)	Case series of 221 admitted Patients (China)	Acute ischemic stroke in 5%, cerebral venous sinus thrombosis in 0.5%, cerebral hemorrhage in 0.5%	
4	Yang et al ⁴² (2020)	52 critically ill adult patients (China)	Headache in 6%	
5	Wang et al ⁴³ (2020)	Case series of 138 hospitalized patients (China)	Dizziness in 9%; headache in 7%	
6	Toscano et al ⁵⁶ (2020)	Case series of 5 patients (Italy)	Flaccid areflexic limb weakness in 80%, facial weakness in 60%	
7	Lechien et al ⁵⁹ (2020)	417 patients (Belgium, France, Italy, Spain, and Switzerland)	Smell dysfunction in 86%, taste dysfunction in 82%	

stroke in COVID-19 patients was ~5% and they postulated elevated levels of C-reactive protein and D-dimer, indicative of an inflammatory state and irregularities with the coagulation cascade, respectively, which might play a part in the pathophysiology of stroke in COVID-19 infection.⁴¹

Sharifi-Razavi et al described a case of intracranial bleeding ensuing in CVA in a 79-year-old COVID-19-positive male who was neither a known hypertensive nor on any anticoagulants that could have caused this event.⁴⁴ The authors postulated that probably dysregulation in the ACE2 receptors leading to cerebral autoregulation disruption and high blood pressure spikes resulted in arterial wall rupture.

Encephalitis

Moriguchi et al described first confirmed case of COVID-19-related viral encephalitis from Japan.⁴⁵ A 24-year-old man presented with headache and fever followed by seizure and episode of unconsciousness. He had neck stiffness; computed tomographic (CT) scan of brain was unremarkable. Cerebrospinal fluid reverse transcription-polymerase chain reaction (CSF RT-PCR) detected SARS-CoV-2. Brain magnetic resonance imaging (MRI) revealed diffusion restriction along the wall of inferior horn of right lateral ventricle, and fluid-attenuated inversion recovery images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus suggestive of encephalitis.⁴⁵

Huang et al reported a case of 40-year-old woman from United States who presented with fever followed by syncope and nasopharyngeal swab on admission was positive for SARS-CoV-2 and afterward CSF was found to be positive for SARS-CoV-2 as well.⁴⁶

Acute Hemorrhagic Necrotizing Encephalopathy

Poyiadji et al described a case of a female patient in her late fifties, presenting with a 3-day history of cough, fever, and altered mental status and subsequently the diagnosis of COVID-19 made by RT-PCR of nasopharyngeal swab specimen.⁴⁷ In this case, testing for the presence of SARS-CoV-2 in the CSF was not done. Noncontrast head CT images demonstrated symmetric hypoattenuation within bilateral medial thalami with a normal CT angiogram and CT venogram. Brain MRI demonstrated hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. Authors suggested this patient might have a cytokine storm syndrome due to severe COVID-19 that resulted in blood-brain barrier breakdown leading to this presentation.

Acute Myelitis

Zhao et al described a case of 66-year-old male from Wuhan city, China, who was admitted for fever and fatigue of 2 days without cough; later on he developed acute flaccid paraparesis with sensory level at T-10 and urinary and bowel incontinence.⁴⁸ All other microbiological studies were negative except for SARS-CoV-2 nucleic acid testing in nasopharyngeal swab. Authors suggested clinical findings could be ascribed to a postinfectious acute myelitis.⁴⁸

Sarma and Bilello reported a case of 28-year-old female who tested positive for COVID-19 via RT-PCR of nasopharyngeal swab and later on diagnosed as longitudinally extensive acute transverse myelitis.⁴⁹

Encephalopathy

Chen et al in a retrospective study of the clinical characteristics of 113 COVID-19 patients from China documented hypoxic encephalopathy in 20 patients.⁵⁰ The incidence was significantly lower in the patients who had recovered. Mao et al described impaired consciousness in 16 (7.5%) patients in their cohort but the diagnostic criteria used were not well-defined.³⁹ Filatov et al reported a case of a 74-year-old male with multiple comorbidities who developed altered mental status after headache, fever, and cough.⁵¹

Seizures

Vollono et al described a case of 78-year-old SARS-CoV-2-positive female patient, who was admitted for focal status epilepticus without any prodromal symptoms in the form of myoclonic jerks of the right side of face and right-sided limbs.⁵² The electroencephalogram discovered semirhythmic, irregular, high amplitude delta activity, mainly lateralized over the left fronto-centro-temporal regions, consistent with focal status epilepticus.

Sohal and Mansur also reported a case of 72-year-old man with comorbidities, who was noted to have multiple episodes of tonic clonic movements of his upper and lower extremities.⁵³

Headache and Dizziness

Headache and dizziness have been reported as minor symptoms associated with presentation of COVID-19 in different studies. The incidence of headache ranges from 6 to 13.1% and dizziness from 9 to 16.8% but the detailed mechanism and pathogenesis have not been discussed.^{39,42,43}

Peripheral Nervous System

Olfactory and Gustatory Impairment

Mao et al reported occurrence of taste impairment (12 [5.6%]) and smell impairment (11 [5.1%]) in their 214 patients cohort.³⁹ Bagheri et al described that anosmia and hyposmia were seen in 48.23% of the respondents, while 83.38% also had a decreased taste sensation.⁵⁴

Guillain-Barré Syndrome

Many cases of Guillain-Barré syndrome (GBS) are now reported that are related to COVID-19. Zhao et al reported a case of 61-year-old Chinese female patient who presented with acute weakness in both legs and severe fatigue. The diagnosis of GBS was made on the basis of clinical examination and electrophysiological studies. She was treated with intravenous immunoglobulin. A week following this, patient developed dry cough and fever; oropharyngeal

swab detected SARS-CoV-2 on RT-PCR assay. Hence, GBS related to SARS-CoV-2 might follow the pattern of a parainfectious profile, instead of the classic postinfectious profile.⁵⁵

Toscano et al reported five patients of GBS with COVID-19. The first symptoms of GBS were lower-limb weakness and paresthesia in four patients and facial diplegia followed by ataxia and paresthesia in one patient. After examination and proper investigation (nerve conduction and CSF studies), GBS was diagnosed and treated accordingly.⁵⁶

Overall, these case reports only propose a likely association between GBS and SARS-CoV-2 infection, and more cases with epidemiological data are needed to support a causal relationship.

Skeletal Muscle Damage

Mao et al reported skeletal muscle injury in 23 of their patients that is 10.7% of cohort.³⁹ Compared with the patients without muscle injury, patients with muscle injury had significantly higher levels of creatine kinase (median, 400.0 U/L vs. median, 58.5 U/L), irrespective of their severity. They have seen that patients with muscle injury had higher neutrophil counts, lower lymphocyte counts, higher C-reactive protein levels, and higher D-dimer levels.

Other Manifestations

Mao et al also described neuralgia in five patients and ataxia in one, but further details were not mentioned.³⁹ Isolated cases of oculomotor nerve paralysis, Miller Fisher syndrome, and polyneuritis cranialis were also described.^{57,58}

Conclusion

Although COVID-19 is mainly a disease of respiratory system, neuropsychological involvement is not uncommon. Neurological manifestations are more in severely ill patients and in some cases can even precede the respiratory symptoms or may be the only symptoms in COVID-19 patients. At present, the full clinical spectrum of patients with COVID-19 with neurological symptoms remains to be categorized. So, there is further need of focused studies.

Conflict of Interest

None declared.

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