

REVIEW ARTICLE

Neurological Manifestations of COVID-19

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ABSTRACT

The year 2020 started with the news of a novel coronavirus, severe acute respiratory syndrome corona virus 2 (SARS-CoV2), induced disease in China which was termed as coronavirus disease 2019 (COVID-19). This viral infection soon became pandemic and affected millions of people all over the world. The virus preferentially affects respiratory system causing dry cough and fever, but has the tendency to spread to different organs in the body leading to multiple organ failure. Recent evidences show that corona virus can invade nervous system and damage it. This review is based on different articles and case reports that provide an evidence of neuro-virulent nature of COVID-19 and its consequences. The neuro-invasive property of the virus is divided into three categories i) Central Nervous System (CNS) manifestations, ii) Peripheral Nervous System (PNS) manifestations and iii) Skeletal Muscle damage. Headache and dizziness were observed to be common symptoms for CNS, whereas loss of smell and taste for PNS damage due to COVID-19. The aim of this review is, to develop an understanding of the devastating effects of COVID-19 on nervous system for the early recognition of virus-induced damage. This information can be used for the development of better therapeutic strategies.

Key Words: ACE2R, COVID-19, Nervous system, SARS-CoV2.

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Introduction

During past three decades the human interventions have led to alterations in different environmental factors which has resulted in the emergence of various novel pathogens. Moreover, the rapid means of transportation have caused these pathogens to spread worldwide.¹ The year 2020 emerged with the report of a novel severe acute respiratory syndrome corona virus 2 (SARS-CoV2) and the disease caused by this virus was termed as coronavirus disease 2019 (COVID-19). The disease started in China and due to spread of this disease to other countries it was declared as global health emergency by World Health Organization (WHO).

The first case of COVID-19 appeared on 31st December 2019, from the individuals who had visited Huanan seafood market, Wuhan in Hubei province of China. Soon the disease became

pandemic, affecting most of the countries.² The SARS-CoV2 is third coronavirus, since 2003, that has zoonotic mode of transmission and has caused respiratory system related morbidity in humans.³ The first corona virus outbreak due to the virus SARS-CoV appeared in the year 2002-2003. This zoonotic outbreak, happened in Guangdong city of China and affected 8098 individuals across 26 countries.⁴ The second corona virus outbreak, resulting from the virus Middle East respiratory syndrome corona virus (MERS-CoV), appeared in 2012. Of all the coronavirus outbreaks the COVID-19 is the most dreadful as it has caused 102,041,000 laboratory confirmed cases and around 2,201,043 deaths (data collected on 29-01-2021 from <https://www.worldometers.info/coronavirus/>). The novel corona virus has more than 79% sequence homology to the SARS-CoV⁵ and therefore, it is named as SARS-CoV-2.⁶

Clinical Manifestations of COVID-19

The SARS-CoV2 preferentially causes respiratory system morbidity and produces pneumonia like symptoms including dry cough, fever, shortness of breath, fatigue and decreased leukocyte count. In severe cases, death of the individual may occur due to acute respiratory distress syndrome. The disease often disseminates in the body and may affect

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multiple organ systems including kidney, heart and nervous system.² Several recent evidence suggest that SARS-CoV2 has ability to invade nervous system and cause neurological complications.⁷

Neuro-invasive Property of SARS-CoV2

In spite of the extensive literature available on pathophysiology of COVID-19, its effects on central nervous system (CNS) are not yet well explored and this aspect largely remains unknown. This is probably due to the reason that neurological symptoms appear later than the respiratory symptoms, and due to severity of respiratory symptoms, the neurological symptoms remain neglected.⁷ But there are several reports that the COVID-19 patients show neurological symptoms including nausea, vomiting, headache and impaired consciousness.⁸ The most prominent evidence for the ability of SARS-CoV2 to invade nervous system is appearance of anosmia (loss of sense of smell) and ageusia (loss of sense of taste). Some scientists even believe that the death due to respiratory failure is not because of its devastating effects on the lungs but, due to damage to the brain.⁹ Moreover, various animal studies¹⁰ and human studies¹¹ have shown the neuro virulence of SARS-CoV. Due to high similarity between SARS-CoV and SARS-CoV-2 it is reasonable to expect that SARS-CoV-2 might also have similar neuro-invasive property. Furthermore, the virus is also isolated from the cerebrospinal fluid (CSF) of the COVID-19 patients¹² which strengthens this assumption. Therefore, this review is focused on the collection of available data on the consequent results of COVID-19 induced neurological damage. An understanding of the SARS-CoV-2 neuro-tropism mechanisms, may not only assist in the timely diagnosis of signs and symptoms of neurological damage but also may help to develop therapeutic interventions to prevent greater damage.

Mechanism of SARS-CoV2 Entry into the Nervous System

The SARS-CoV and SARS-CoV-2, due to their striking similarity, gain entry into the cell using same receptor named as angiotensin converting enzyme 2 (ACE2). Although the expression of ACE2 is very low in the brain¹³ but SARS-CoV infection is also reported in the areas of brain that have very low ACE2 expression, even in normal conditions.¹⁴ Therefore, it has been proposed that ACE2 alone is not

responsible for making a cell susceptible to virus entry but might involve other entry pathways as well. But the exact mechanism of SARS-CoV entry into the brain is not clearly understood. Moreover, the route taken by the virus to reach to the brain is also under discussion and different routes are proposed (Figure 1).

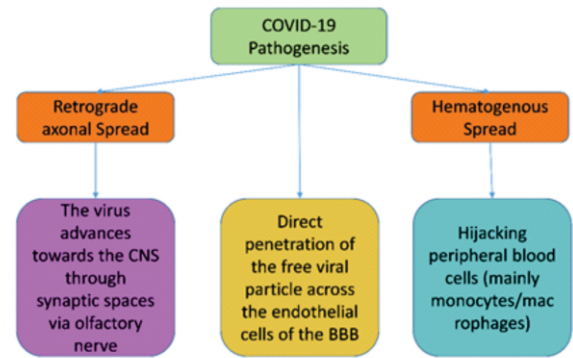


Fig 1: Different mechanisms proposed for the entry of SARS-CoV2 into the nervous system

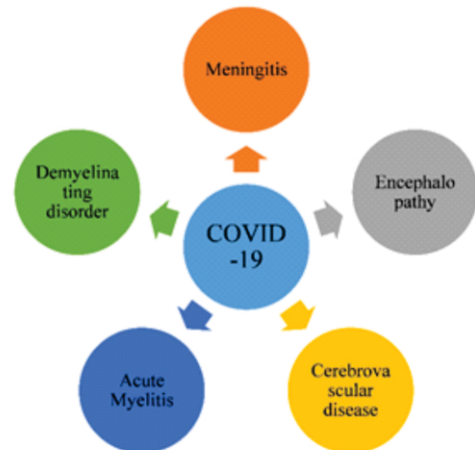


Fig 2: Different nervous system complications manifested by COVID-19

Due to unavailability of literature on neurotropism of SARS-CoV2, most of the speculations are made on the basis of the information available about the SARS-CoV. Due to great similarity between both viruses it is assumed that the facts known about SARS-CoV may be extrapolated to SARS-CoV-2.

Retrograde Axonal Spread

In previous experiments it was observed that intranasal inoculation of SARS-CoV particles, in mouse, resulted in the presence of virus in brain stem and thalamus. It was observed that viral particles spreading occurred via olfactory nerve.¹⁰ Similar route of transmission is also proposed for

SARS-CoV-2 termed as retrograde axonal transport. In this pathway, the virus disrupts the nose epithelium and invades peripheral nerve terminal and advances towards the CNS via synapses. The retrograde axonal transport pathway is supported by the fact that the viral particles are found to be present in nasal epithelium and olfactory bulb of COVID-19 patients. Moreover, anosmia in COVID-19 patients is also a major factor to believe that the virus has ability to travel, to CNS, via retrograde axonal pathway.¹⁵ However, this route needs to be validated due to the fact that the olfactory bulb does not express ACE2 receptor.¹⁶

Direct Viral Particle Penetration in Brain

Another proposed route of viral penetration to brain is via direct disruption of the blood brain barrier. As the ACE2 receptor is expressed in the capillary network of blood brain barrier. Therefore, owing to the binding of SARS-CoV2 spike protein to the ACE2 receptor, it can be expected that the status of blood brain barrier will be altered. Although the evidence for this mode of dissemination is only available in *in-vitro* model and needs to be validated *in-vivo*. In a study on the advanced micro-fluid 3D model of the human blood brain barrier it was observed that spike protein of SARS-CoV2 has the ability to disrupt the blood brain barrier (BBB) integrity. In this study, the test model was perfused with S1 spike protein of SARS-CoV2 (50 nM, for two hours). The control BBB model was left untreated. After treatment completion the BBB permeability was measured, with perfusion of Fluorescein isothiocyanate (FITC) conjugated dextran, which revealed a three times increased permeability coefficient in the model treated with SARS-CoV2 spike protein. This caused a substantial leakage through treated vessels. Moreover, reduced expression of the zona occludin, the protein responsible for tight junction formation, was also observed in treated vessels.¹⁷

Hematogenous pathway

It has been reported that the coronaviruses have the ability to hijack peripheral blood cells and invade nervous system via hematogenous pathway. The peripheral blood cells, infected during the acute viremic phase, may transmigrate to brain, via paracellular route, between BBB endothelial cells.¹⁸ Moreover, different coronavirus strains, including SARS-CoV2, can infect immune system cells and

when these infected immune cells are recruited to the coronavirus infected brain tissue, these immune system cells can act as reservoirs for neuro-invasion of virus.¹⁹

Causes of Nervous System Damage Due To Covid-19

Following ways are proposed for COVID-19-induced damage to the nervous system.

Hypoxic injury

The respiratory tract infection due to SARS-CoV2 may cause respiratory insufficiency and consequently hypoxia. The hypoxic state may lead to anaerobic metabolism in brain resulting in accumulation of toxic substances in the brain that causes brain damage. This hypoxia induced damage is manifested by the appearance of neural edema and cerebral swelling.²⁰

Immune system mediated injury

The immune system mediated injury is caused by the mechanism known as cytokine storm. After the initial infection by virus, the excess amount of cytokines are released which in turn further activates macrophages and lymphocytes.²¹ The overproduction of cytokines causes over activation of complement system which might lead to intravascular coagulation and consequently multi-organ failure.²²

Cerebrovascular injury

Binding of SARS-CoV2 to ACE2 receptors, in endothelial cells of BBB, results in an increase in the cerebral vessels pressure that might lead to intracerebral hemorrhage.²³ Moreover, impairment in the coagulation cascade also leads to intracranial hemorrhage in patients severely ill with COVID-19.²⁴

Neurological manifestations of COVID-19

The symptoms from SARS-CoV2 infection may range from mild flu-like to more severe manifestations that may lead to failure of multiple organ systems. Various studies on the clinical cases have revealed that neurological manifestations may fall in one of the following categories, (I) central nervous system (CNS) symptoms (II) Peripheral nervous system (PNS) symptoms and (III) skeletal muscle symptoms. The clinical data reveals that most common CNS symptoms are headache and dizziness while most common PNS symptoms are loss of sense of smell and taste. The overall neurological deficits caused by COVID-19 are summarized in Table 1.

Table 1: Nervous system manifestations of COVID-19 infection

Authors	Study design	Patients enrolled	Mean age (years)	Headache and dizziness	Impaired consciousness	Hyposmia and Hypogeusia	Skeletal muscle injury
Mao et al ²⁵	Retrospective	214	52.7	31.9%	14.8%	5.1% 5.6%	19.3%
Helms et al ²⁶	Prospective	58	63	-	-	-	-
Yin et al ²⁷	Retrospective	106	72	16%	16%	-	24.5%
Giacomelli et al ²⁸	Cross-sectional	59	60	3.4%	-	18.6%	-
Bagheri et al ²⁹	Cross-sectional	10069	32.5	-	-	83.3%	-
Yan et al ³⁰	Cross-sectional	59	45	66.1%	-	68% (hyposmia) 71% (hypogeusia)	63%

Central Nervous System Manifestations of COVID-19

The most notable and devastating CNS complications includes meningitis/ encephalitis, encephalopathy, cerebrovascular disease, acute myelitis and demyelinating disorder. The summary of reported cases, after SARS-CoV2 infection, for these complications is presented in Table 2.

Peripheral Nervous System Manifestations of Covid-19

It has been reported loss of sense of smell (anosmia) or loss of sense of taste (ageusia) are the most common peripheral nervous system complications

Table 2: Central Nervous system manifestations of COVID-19

Age/Gender	Complication	Location	References
-	Encephalitis	Beijing, China	Xiang et al ³¹
24 year/ Male	Meningitis/Encephalitis	Yamanashi, Japan	Moriguchiet al ³²
Male	Encephalitis	Wuhan, China	Ye et al ³³
40% of patients in study cohort	Headache and Encephalopathy	Wuhan, China	Mao et al ²⁵
74 year/ Male	Encephalopathy	USA	Filatov et al ³⁴
58 year/ Female	Acute Hemorrhagic Necrotizing Encephalopathy	USA	Poyiadji et al ³⁵
Six patients out of cohort of 214 patients	Cerebrovascular disease	Wuhan, China	Mao et al ²⁵
Three patients in study cohort	Ischemic stroke	France	Helms et al ²⁶
79 year/ Male	Intracerebral Haemorrhage	Iran	Sharifi et al ³⁶
66 year/ Male	Acute Myelitis	Wuhan, China	Zhao et al ³⁷
54 year/ Female	Demyelinating lesions	Italy	Zanin et al ³⁸

Table 3: Peripheral Nervous system manifestations of COVID-19

Age/ Gender	Presentation and Diagnosis	Location	References
30 years	anosmia, ageusia and Mild flu	Denmark	Haldrup et al ³⁹
Female (60 years)	1. Anosmia, ageusia.	Oslo, Norway	Hjelmesæth and Skaare ⁴⁰
Male (60 years)	2. Anosmia, ageusia.		
Male (90 years)	3. Anosmia, dysgeusia, cough, dyspnea, and fever		
female (59 years)	Hypogeusia and hyposmia progressed to anosmia	Pennsylvania, USA	Melley et al ⁴¹
Female (66 years)	Guillain- Barre syndrome diagnosed on the basis of fatigue and lower limb Weakness	Jingzhou, China	Zhao et al ⁴²
Male (65 years)	Guillain-Barre syndrome diagnosed on the basis symmetric ascending quadriparesis which was found to be acutely progressive.	Sari, Iran	Sedaghat and Karimi ⁴³
Male (54 year)	High fever, diarrhea and dry cough accompanied by lower limb Weakness and numbness that resulted in inability of patient to move. Diagnosis: Guillain-Barre syndrome	USA	Virani et al ⁴⁴
Five patients	Guillain-Barre syndrome diagnosed on the basis of limbs Weakness, face diplegia, flaccid tetraplegia and ataxia.	Italy	Toscano et al ⁴⁵
1. Male (50 years), 2. Male (39 years)	1. Miller Fisher syndrome diagnosed on the basis of Ageusia, areflexia, ataxia and right fascicular oculomotor palsy 2. Mild fever and diarrhea followed by Ageusia, areflexia and bilateral abducens palsy. Diagnosis: Miller Fisher syndrome and polyneuritis cranialis.	Madrid, Spain	Gutiérrez-Ortiz et al ⁴⁶

of the COVID-19. These two complications are considered even stronger indications of infection by SARS-CoV-2.²⁵ Very rarely some severe complications like Miller Fisher syndrome and Guillain Barre Syndrome are also manifested in case of COVID-19. The available reports on the peripheral nervous system manifestations of COVID-19 infection are summarized in Table 3.

Skeletal Muscle Injury due to COVID-19

The mechanism of skeletal muscle injury due to COVID-19 is not well understood but it is assumed that presence of ACE2 receptor on the muscles plays an important role in the viral entry and causing damage to the muscles.⁴⁷ The ACE2 receptors are reported to have a beneficial role in regulation of regulation of skeletal muscle function.⁴⁸ Another proposed mechanism is that the cytokine storm resulting from SARS-CoV2 infection might be the reason for observed muscle damage and consequently organ failure.⁷ In patients having severe symptoms of muscle injury have lesser number of lymphocytes and higher level of C reactive protein in the blood which depicts increased inflammatory response. This higher inflammatory response consequently leads to muscle damage which is depicted by high creatine kinase level that, in severe cases, may lead to multiple organ dysfunction/failure.^{7,25}

Conclusion

The clear understanding of neuro-invasive and neuro-virulent character of COVID-19 needs to be addressed on priority basis, to avoid major complications in COVID-19 patients. These complications might appear after the primary symptoms, like fever and cough, subside. Therefore, a clear understanding of the molecular and cellular mechanisms, through which the COVID-19 affects nervous system, may help in planning prognostic indication and developing strategies for better therapeutic interventions. Moreover, a widespread awareness about neurotropism of COVID-19 may help in early recognition of the symptoms of virus-induced damage to nervous system.

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