REVIEW ARTICLE

# Neurological Manifestations of COVID-19

Syeda Mehpara Farhat

**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-CoV[5] 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

*Department of Biological Sciences*
*National University of Medical Sciences, Rawalpindi*
*Correspondence:*
*Dr. Syeda Mehpara Farhat*
*Assistant Professor, Biological Sciences*
*National University of Medical Sciences, Rawalpindi*
*E-mail: mahpara.farhat@numspak.edu.pk*

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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 studies[10] and human studies[11] 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 form the cerebrospinal fluid (CSF) of the COVID-19 patients[12] 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 brain[13] 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).

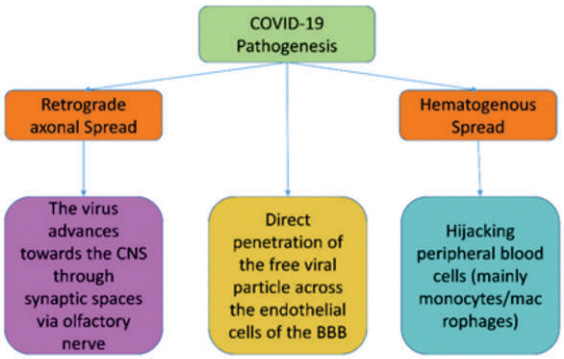


**Fig 1: Different mechanisms proposed for the entry of SARS-CoV2 into the nervous system**

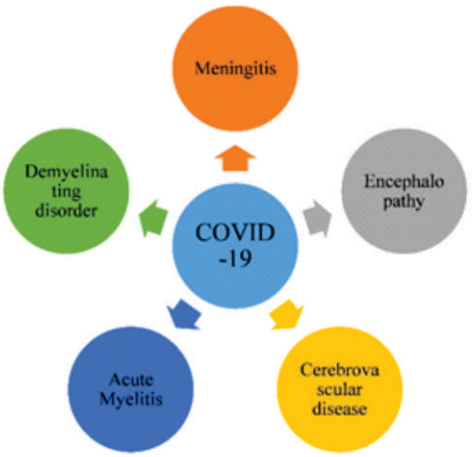


**Fig 2: Different nervous system complications manifested by COVID-19**

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 | Moriguchi et 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 | Cerbrovascular 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 Myelitus | 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) Male (60 years) Male (90 years) | 1. Anosmia, ageusia. 2. Anosmia, ageusia. 3. Anosmia, dysgeusia, cough, dyspnea, and fever | Oslo, Norway | Hjelmesæth and Skaare[40] |
| 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 complication are considered even stronger indications of infection by SARS CoV-2.[25] Very rarely some severe complications like Miller Fischer 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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