SHORT REPORT

# Misfortune and spy story in the neurological manifestations of Covid-19

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## Abstract

Covid-19 is associated with different neurological manifestations. About one third of Covid-19 patients have some neurological disorders as paresthesia, headache, cold extremities and disturbances of consciousness, which are more evident in severely affected patients. These neurological manifestations may coexist or precede the onset of respiratory manifestations by about 2-3 weeks. Acute ischaemic stroke (AIS) and associated brain damage may develop due to acute respiratory distress syndrome (ARDS) induced-hypoxia. Prolonged hypoxia in late-stage Covid-19 leads to vasodilatation, intracranial hypertension, brain oedema, and AIS. In view of substantial evidence, this perspective explores the potentially direct or indirect effect of SARS-CoV-2 on the Central Nervous System of patients with COVID-19 pneumonia. The AIS is the end of most Covid-19-induced neurological complications. Covid-19 can lead to various neurological manifestations due to involvement of CNS directly through olfactory neurons or indirectly through induction of cytokine storm.

**Keywords:** Covid-19, Acute respiratory distress syndrome, Acute ischemic stroke.

## Introduction

Coronavirus disease 2019 (Covid-19) is a global pandemic caused by the novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). initially called Wuhan viral pneumonia.[1] On 11th of March, 2020 Covid-19 was declared as a pandemic with the need of urgent intervention via rapid socioeconomic efforts. Covid-19 lead to disastrous effects internationally involving more than 183 million individuals with 4 million confirmed deaths till early July 2021.[2] Covid-19 is associated with different neurological manifestations, Mao et al found that about one third of Covid-19 patients have some neurological disorders, including paresthesia, headache, cold extremities and disturbances of consciousness that are more evident in severely affected patients.[3] In addition, SARS-CoV-2 may lead to viral encephalitis, brain oedema and neuronal degeneration with risk of peripheral neuropathy.[4] In Covid-19, the neurological manifestations of infected patients have not been adequately reported. As elderly people can have altered level of consciousness, it can cause confusion in differentiating it from the neurological complications of Covid-19. Al-kuraishy et al., confirmed that about 6% of Covid-19 patients presented with acute ischaemic stroke (AIS), 15% with disturbances of consciousness, and 19% with movement disorders due to endothelial injury-induced coagulation disorders and development of cytokine storm.[5]

It has been established, that SARS in 2003 and Middle East Respiratory Syndrome (MERS) in 2012 were associated with neurological complications including AIS, encephalitis, polyneuropathy, and seizures. These neurological manifestations may coexist or precede the occurrence of respiratory manifestations in about 2-3 weeks.[6] The genome of SARS-CoV-2 has about 80% similarity with that of SARS-CoV genome; hence it is logical to incriminate SARS-CoV-2 in the pathogenesis of neurological disorders of Covid-19.[7]

In fact, SARS-CoV-2 does not cross the blood brain barrier (BBB), however secondary bacterial infections in Covid-19 pneumonia may cause damage to the BBB that facilitate viral entry to the meninges and brain tissue. Moriguchi et al report a first case of SARS-CoV-2-induced meningitis /encephalitis in which nasopharyngeal swab for SARS-CoV-2 RNA was negative, while it was positive in cerebrospinal fluid (CSF).[8] Moreover, viral pneumonia is deeming as an independent risk factor for AIS due to cytokine storm, which increases the risk of AIS and haemorrhagic stroke.[9] Al-kuraishy et al confirmed that AIS-induced pro-inflammatory and inflammatory reactions may contribute to further ischaemic changes leading to the poor neurological outcomes in the post-stroke era.[10] Thereby an early detection of focal neurological deficit in Covid-19 patients and prompt management may prevent inflammatory induced-post-stroke neurological complications.

The plausible scenario of Covid-19 mediated brain injury is that SARS-CoV-2 may enter BBB, CSF and brain tissues through motor or sensory neuron endings through

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retrograde transmission.[11] SARS-CoV-2 as other coronaviruses mainly affects olfactory neurons of the olfactory bulb at first and through this pathway may enter the CSF and brain.[12] This explains the cause of anosmia, occuring at an early stage of Covid-19 (91% before hospitalization), due to reversible degeneration of olfactory neurons. Therefore, SARS-CoV-2 reaches the brain within seven days through olfactory neurons via retrograde neuronal transmission.[13] Therefore removal of olfactory bulb in the experimental animals attenuate brain invasion by SARS-Co-V. The selective affinity of SARS-CoV-2 to the olfactory bulb is due to the over-expression of angiotensin converting enzyme 2 (ACE2) at the olfactory neurons, regarded as a receptor and entry-point of SARS-CoV-2.[14]

Indeed the cellular transmembrane serine protease 2 (TMPRSS2) is also expressed in the olfactory neurons, which involve in trimming of surface protein (SP) of SARS-CoV-2.[15] These findings explain the neuronal pathway for the transmission of SARS-CoV-2 to the brain. The binding of SARS-CoV-2 to ACE2 in the cerebral endothelial cells, provoke cerebral vasoconstriction through inhibition of the vasodilator effect of ACE2, leading to cerebral ischaemia and activation of inflammatory cascades.[16]

A scoping review showed that AIS and associated brain damage may develop due to acute respiratory distress syndrome (ARDS)-induced hypoxia as prolonged hypoxia in late-stage Covid-19 leads to vasodilatation, intracranial hypertension, brain oedema, and AIS.[5] Therefore, continuous oxygen therapy in patients with Covid-19 pneumonia may prevent neurological complications even in the early stage of the disease. As of yet, SARS-CoV-2-induced cytokine storm as evident by higher release of pro-inflammatory cytokines leading to BBB damage with further activation of brain glial cells to secret IL-6, forming a vicious cycle ending with AIS and brain injury.[17]

**Neurological manifestations of COVID-19:** Clinical data from 214 patients with COVID-19 demonstrated neurological symptoms in 36.4% of patients reported by Mao et al,. These included, anosmia, hyposmia, ageusia, hypogeusia, ataxia, seizure, neuralgia, and stroke. Stroke and other cerebrovascular disorders as well as altered consciousness are correlated with Covid-19 severity. Besides, some less specific neurological manifestations that are commonly observed in other viral infections are also reported like headache and myalgia, present in 8% and 12% of Covid-19 patients respectively.[18] Of interest, severe headache in Covid-19 patients without neurological deficit might due to release of pro-inflammatory cytokines and development of inflammatory burst. However, headache might be a sign of meningeal irritation due to CNS involvement rather than to the systemic reaction mainly when it is associated with focal neurological deficit.[19] An observational study by Ong et.al. involving 138 Covid-19 patients, illustrated that fatigue is the most common neurological manifestation found in 69.6% followed by myalgia in 34.8% and headache in 6.5% at time of admission.[20] Likewise, Chen et al., observed that headache is present in 8% and confusion in 9% of Covid-19 patients at time of hospitalization.[21] Furthermore, SARS-CoV-2 infection may present as peripheral neuropathy, motor or sensory and some cases mixed motor-sensory neuropathy.[22]

**Mechanism of neuronal injury in Covid-19:** The underlying mechanism for involvement of peripheral and CNS in Covid-19 is linked to the expression of ACE2.

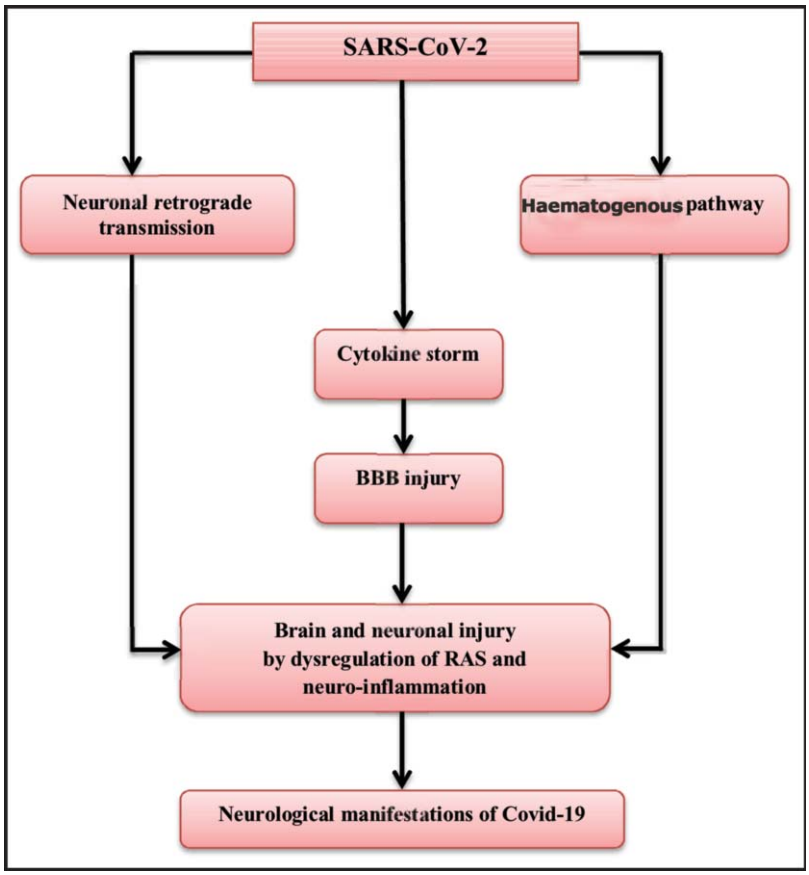


**Figure:** Mechanism of neurological manifestations in Covid-19: SARS-CoV-2 through retrograde neuronal and haematogenous transmission leads to direct brain injury. SARS-CoV-2 through induction of cytokine storm may cause injury of blood brain barrier (BBB). Dysregulation of renin-angiotensin system (RAS) and neuro-inflammations lead to neurological manifestations of Covid-19.

It has been reported that ACE2 is highly expressed in neuronal, glial and astrocyte cells intricate in the regulation of brain functions through autoregulation of cerebral blood flow, control of autonomic and neuroendocrine functions.[23] Dysregulation of systemic and/or neuronal renin-angiotensin system (RAS) due to down-regulation of ACE2 by SARS-CoV-2 together with neuro-inflammation and hypoxia might be the potential mechanisms of neurological manifestations in Covid-19.[24] Moreover, SARS-CoV-2-induced peripheral neuropathy like Guillian-Barre syndrome had been observed in Covid-19 patients which could be due to hypoxaemia, pro-inflammatory and immunological reactions.[25]

In the light of substantial body of evidence, this report explores and sheds light on the potential direct or indirect effect of SARS-CoV-2 on the CNS in patients with Covid-19. Direct interaction between SARS-CoV-2 and neurons with induction of neuro-inflammations may explain the spectrum of neurological manifestations in Covid-19 patients (Figure). In this concern, extensive studies are mandatory to explore the precise interaction between SARS-CoV-2 and neurons to verify the mechanistic target therapy.

## Conclusion

Covid-19 leads to various neurological manifestations due to involvement of CNS directly through olfactory neurons or indirectly through induction of cytokine storm.

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