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**Review Article**

# NEUROLOGICAL MANIFESTATIONS OF COVID-19: A REVIEW

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***Abstract:*** ***The pulmonary manifestations of COVID-19 have been well described in the literature. Emerging evidence suggests COVID-19 has neurologic consequences as well. A few case reports have described neurological complications in patients with COVID-19. Viral neuro invasion could plausibly be achieved by several routes. Patients show many symptoms as described here, however, it remains unknown to what extent SARS-CoV-2 damages the central nervous system or if neurological symptoms are attributable to secondary mechanisms.***

**Key words:** COVID-19, Neurological diseases

## INTRODUCTION

Severe acute respiratory distress syndrome corona virus-2 (SARS-Covid-2 or Covid-19) emerged from Wuhan, China in Dec. 2019 causing severe pulmonary manifestations which have been well described [1-3]. There is growing evidence of neurological complications of patients with covid-19 disease [4]. Two similar human corona viruses, Middle East respiratory syndrome (MERS- COV-2) and severe acute respiratory syndrome (SARS-COV-1) have also been associated with neurological disease in rare cases. This raises question of whether it contributes to post infectious neurologic complications [4]. There have been case reports describing neurological complications in patients with COVID-19. However it remains unknown to what extent SARS-COV-2 directly damages the CNS or due to secondary

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***Dedication:*** *We are very happy and honoured to dedicate this paper to Prof P.D. Gupta at this auspicious occasion of his 81st birthday, whose academic career we deeply admire.*

mechanisms. Coronaviruses (COV.) are large enveloped positive sense RNA viruses divided into 3 genera, Alpha, Beta and Gamma. These viruses infect humans and numerous animal species generally causing upper or lower respiratory tract, gastro-intentional, neurological or hepatic disease.

Beta corona viruses SARS-COV-2, SARS-COV-1 and MERS COV. are associated with severe disease in humans although human corona viruses (HCOV) are typically associated with respiratory disease [4]. 3HCOV have shown to infect neurons. HCOV-229E, HCOV-OC-43 and **SARS COV-1.** The neuroinvasive potential of HCOV-OC-43 has been particularly well studied. It has been shown to thrive in neural cells in vitro cultures [5]. Oligodendrocytes, astrocytes, neuralgia and neurons are susceptible to acute infection with HCOV-OC-43 and all except neuralgia support persistent infection. HCOV-OC-43 can invade CNS intranasally which is followed by rapid spread throughout the CNS [5]. Neuronal damage appears to be caused by direct virus mediated and not due to immune mediated injury. The CNS damage causes a range of neurological disorders including encephalitis, stroke and transient flaccid paralysis etc.

**SARS-COV-1& MERS-COV:** During the SARS COV-1 pandemic 2002-2003& MERS COV.2012 pandemic neurological manifestations were reported in some patients e.g. Guillain-Barré (GB) syndrome, Acute motor axonal neuropathy (AMAN), Ischemic stroke, Seizures, Acute disseminated encephalomyelitis (ADEM), Encephalitis and Bickerstaff encephalitis.

**SARS-COV- 2:** The SARS-COV-2 virus shows close sequence homology to SARS-COV-1. Both viruses use spike proteins on the viral surface to bind the angiotensin converting enzyme-2 (ACE-2) receptors on mammalian host cells, then use serine protease transmembrane protease serine 2 to prime spikes. In humans ACE-2 is expressed in air way epithelia, kidney cells, small intestine, lung parenchyma, widely throughout the CNS and vascular endothelia thought out the body. ACE 2 is expressed in neurons, astrocytes and Oligodendrocytes, expression of ACE-2 was also highly concentrated in the Substantia nigira, ventricles medial temporal gyrus, posterior cingulate cortex and olfactory bulb. Wide spared ACE-2 expression in the brain raises the concern that SARS COV-2 similarly to SARS-COV-1 has the potential to infect neurons and glial cells throughout the CNS [4].

**Potential mechanism of invasion:** Although there are reports of neurological complications of COVID-19 but it is unclear if SARS COV-2 is neurotropic in humans. Viral neuroinvasion could plausibly be achieved by several routes including trans synaptic transfer across infected neurons, entry vial olfactory nerves. Infection of vascular endothelium or leucocyte migration across the blood brain barrier may also be one of the routes.

**Neurological manifestations:** Information about the neurologic manifestations in patients with COVID19 is sparse.Currently there are number of published case reports and clinical studies [6-9]. A systematic study in Wuhan, China reported neurologic findings in 214 patients hospitalized with COVID-19. Another symptomatic study in France reported neurological symptoms in 49 out of 58 patients including confusion, encephalopathy and corticospinal tract signs on examination as well as leptomeningeal enhancement and perfusion abnormalities on magnetic resonance imaging [7].The most common neurologic symptoms in COVID-19 are headache, anosmia and ageusia. Other neurol-ogical manifestations include stroke, encephalopathy, coma and seizures [9].

**Headache:** Headache is one of the most common initial complaints in patients with COVID-19. The recent study from India headache was a predominant complaint along with fever, cough sore throat and breathlessness. Headache can occur up to one third of diagnosed patients of COVID-19.

Headache is a well described symptom of meningitis, encephalitis, vasculitis and intra cranial hypertension. Less is known about its pathophysiological connection with COVID-19. Neuro inflammatory mechanisms have been implicated in headache syndromes. Release of cytokines during various stages of COVID-19 infection lead to similar mechanisms for headache [9].

**Anosmia and Ageusia:** Anosmia has been noted in almost all respiratory viral infections such as influenza and it's associated with nasal swelling and congestion, however in COVID -19 anosmia is typically not associated with nasal swelling or rhinitis. Patients presenting with anosmia as an early symptoms should

be tested for COVID-19 infection. The prevalence of anosmia and ageusia ranges widely 5-88% in the literature [11].

**Impaired consciousness**: Altered sensorium has been reported in 37% patients hospitalized due to COVID-19 infection [6]. There are several possible mechanisms of impaired consciousness including invasion and damage of brain parenchyma, seizures, toxic metabolic encephalopathy and demyelinating disease.

**Seizures**: Patients of primary seizure disorder are at high risk of break through seizures and status epilepticus. Sub clinical seizures are reported in roughly 10% of patients with critical illness due to COVID 19. This may be probably due to decreased seizure threshold [13].

**Encephalitis:** SARS-COV2 can invade CNS like SARS-COV-1 and MERSCOV and cause encephalitis. However, currently there is no direct evidence of encephalitis secondary to SARS-CoV2. A suspected case of meningoencephalitis in a patient with COVID-19 was reported in Japan [12].

**Toxic metabolic encephalopathy:** Encephalopathy is characterized by impaired consciousness and arousal. Presenting with confusion, lethargy and delirium, common risk factors that predispose patients to encephalopathy are advanced age, underlying dementia. Multiplecomorbidities, infection, severe medical illness, malnutrition and various metabolic and endocrine disturbances are the symptoms of this diseases.

Patients hospitalized with COVID-19 may exhibit numerous toxic metabolic derangements including cytokine storm, severe inflammation, sepsis and renal dysfunction. COVID-19 disease in characterized by increased IL2, IL-6, IL-7 granulocyte, colony stimulating factor, interferon gamma γ inducible protein 10, monocyte chemoattractant protein macrophage inflammatory 1-α and tremor necrosis factor 1 a. Cytokines storm likely contributes significantly [10].

**Stroke:** Mao et al. [6] reported that 5% of a hospitalized cohort in Wuhan had acute stroke, including intra cerebral hemorrhage and cerebral sinus venous thrombosis. Patients who had stroke were significantly older, had more cerebrovascular risk factors and had significantly higher CRP and D-Dimmer level suggesting hypercoagulable state. However a study at Mount Sinai Hospital New York suggested that young patients (<50 years) developed large vessel strokes in COVID-19 infection, suggesting that all ages are at risk of developing stroke[4].

**GB Syndrome and Peripheral Nerve Disorder:** GB syndrome also known as acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) can develop after any viral infections. This is thought to occur through a molecular mimicry mechanism in which infecting viruses likely share epitopes similar to components of peripheral nerves, which stimulates autoreactive T or B cells. The antibodies produced by the immune system to fight the virus cross react and bind to components of the peripheral neurons system causing neuronal damage and dysfunction. Both AIDP and AMAN variants have been documented after COVID-19 infection. Cases of AIDP, AMAN and Bickerstaff encephalopathy have been reported in the setting of MERS-COV-1. Reports of GBS in patients with COVID-19 are emerging [15-17]. Italian case series of COVID-19 reported 5 patients of GBS. Gutiérrez-Ortiz et al. [18] also reported patients with AMAN and Millar Fisher variant of GBS.

**Spinal cord:** A clinical of case of typical tansverse Myelitis has been reported from Wuhan but MRI and CSF findings were not available (9)

**Treatment:** Possible therapies for COVID-19:- Although there is no definitive drug therapy available for the treatment of COVID 19 infection. However, currently some drugs have been tried in patients with severe COVID -19 disease.

**Hydroxychloroquine:** Hydroxychloroquine (HCQ) works by preventing acidification of endosome, which interrupts cellular functions and may prevent viral entry via ACE-2 binding. HCQ can cause cardiotoxicity. Neurological side effect such as peripheral neuropathies, neuromyopathy, retinopathy and may worsen myasthenia gravis. It also lower seizure threshold [19].

**Tocilizumab:** Tocilizumab is a monoclonal antibody to all the IL-6 receptors that may attenuate cytokine release in patients with severe inflammatory disease [20]. There are limited data that suggest possible benefits. Tocilizumab may cause headache and

dizziness and multi focal cerebral thrombotic microangiopathy. Recently we have seen tocilizumab induced ADEM in one patient.

**Remdesivir;** Remdesivir is a viral RNA-dependent RNA polymerase inhibitor. In vitro data have shown that it is a potent SAR-COV-2 inhibitor and early studies have shown some benefit. Clinical trials are ongoing which will provide valuable data [21].

**Convalescent plasma therapy :** Some people with COVID -19 infections become very sick and develop ARDS and multi organ involvement. Convalescent plasma therapy may be helpful for patients with COVID-19 who do not helped by other treatments. Preliminary studies have shown encouraging results.

Many patients with neurological disorders such as multiple sclerosis, NMO spectrum disorders, autoimmune encephalitis, CIDP and neuromuscular junction disorders such as myasthenia gravis or Lambert Eaton syndrome and polymyositis need immune suppressive therapies which can put them at further risk of severe COCID-19.. These patients are advised to continue with immuno-modulatory therapies. However these patients need extra vigilant, social distancing and they should be advised telemedicine visits [22-24].

## CONCLUSION

COVID-19 (SARS-COV-2) has infected millions and affected billions of lives. The understanding of neurologic disease is in patients with COVID-19 is evolving and clinicians should continue to monitor patients closely for neurological disease. Early detection of neurological deficits may lead to improved clinical outcome and better treatment algorithms. Further clinical and laboratory data such as nervous system imaging, CSF analysis and histopathology will be essential in understanding the pathophysiology and potential for CNS injury. Lastly regular follow ups and neurological assessment of patients after recovery will be crucial in understanding the natural history of COVID-19 in the nervous system and monitoring for potential neurologic sequelae.

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