

## Neurological profile in COVID-19: A review

Amit Ranjan Barua<sup>1</sup>, Dhrubajyoti Choudhury<sup>2</sup>, Jai Prakash Sharma<sup>3</sup>, Pari Kemprai<sup>4</sup>

<sup>1</sup> Consultant Neurologist, Department of Neurology, GNRC Medical, Sila Grant, North Guwahati, Guwahati, Assam, India

<sup>2,4</sup> Senior Resident, Department of Neurology, GNRC Medical, Sila Grant, North, Guwahati, Guwahati, Assam, India

<sup>3</sup> Deputy Consultant, Department of Neurology, GNRC Medical, Sila Grant, North, Guwahati, Guwahati, Assam, India

### Abstract

Since the outbreak of SARS-CoV-2 or COVID-19 from Wuhan, China in December, 2019 it has become a global pandemic in an alarming pace. Though it is primarily a respiratory illness, it has been found to have the propensity to cause neurological manifestations. It's interesting to note that neurological presentations were more common in those patients who do not present with typical symptoms of COVID-19. Through this review article, we tried our humble gesture to highlight the varied neurological profile or manifestations that occur due to the illness which have been recorded by various authors across the globe for the purpose of upgrading the awareness of the treating physician.

**Keywords:** nervous system, COVID-19, neurotropism, encephalitis, guillain barre syndrome, stroke

### 1. Introduction

The World Health Organization (WHO), officially declared the recent SARS-CoV-2 or COVID-19 a pandemic on March 11, 2020 and is spreading worldwide in an alarming pace.

The amount of research and number of review articles being published on COVID-19 is extensive because it has created curiosity among all the sections of the society across the globe.

During its initial days, it was thought that it primarily affects the respiratory system, but as case numbers of COVID-19 continued to rise across the globe, the medical community started seeing an increasing number of reports of neurological symptoms. Some studies report that over a third of patients show neurological symptoms<sup>[1]</sup>.

COVID-19 is not unique in being a respiratory virus that can also attack the nervous system.

Influenza, measles and other respiratory syncytial viruses can all attack the central nervous system<sup>[1]</sup>. Other coronaviruses have also been found to attack the nervous system and cause neurological disorders. The related seasonal coronavirus, HCoV-OC43, typically causes mild respiratory symptoms but can also cause encephalitis in humans. Similarly, MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome) viruses can cause severe neurological diseases which is widely known<sup>[1]</sup>.

It has been estimated that COVID-19 causes 6-36% incidences of neurological events during the course of the illness<sup>[2]</sup>.

### 2. Proposed Mechanisms of Nervous System Involvement

As there is not enough experimental data available for COVID-19 regarding the mechanisms of involvement of the nervous system, but it is considered that as it is similar to SARS and MERS Viruses, it is considered and expected that it will behave in a similar manner<sup>[1]</sup>.

#### a. Neurotropism

Corona viruses are not primarily neurotropic viruses and their primary target is the respiratory epithelium. The target receptor for attachment to cell and subsequent internalisation is through the angiotensin converting enzyme-2 receptor (ACE 2). After entry into the cell, the viral RNA is released in the cell cytoplasm and subsequently translated and replicated, after formation of envelope protein and incorporation of RNA, it is released in the circulation<sup>[2]</sup>. ACE 2 receptors are also found in glial cells in the cerebral and spinal neurons. Hence it can attach, multiply and damage the neuronal tissue. Some studies have suggested that it invades the cerebral neurons via retrograde transfer via olfactory epithelium /neuron. Also during the acute phase of viremia, due to the disruption or increased permeability of blood brain barrier (BBB), it can gain access to the cerebral neurons, Another postulated mechanism is the invasion of peripheral nerve terminals and then gains entry into the central nervous system (CNS) through the synapse connected routes<sup>[2,3]</sup>.

#### b. Hypoxia related cerebral injury

COVID-19 is widely known to cause respiratory insufficiency. The interesting thing about the possible propagation mechanism is the presence of the virus in the brain stem, because this structure contains nuclei that regulate the respiratory rhythm. Respiration is controlled by the regulation of a number of neural groups. Through the nucleus of the solitary fascicle, the CNS receives information from the chemoreceptors that detect changes in the concentrations of CO<sub>2</sub> and O<sub>2</sub>, alterations in these components lead to an increase or decrease in the respiratory effort. The entry of COVID-19 into this structure could affect the respiratory system by alteration of these neuronal groups leading to hypoxia<sup>[4, 5, 6]</sup>. Therefore, hypoxia needs to be considered among the major putative mechanisms of cerebral injury which may be due to peripheral vasodilatation, hypercarbia, hypoxia and

anaerobic metabolism, oxidative damage resulting in cytotoxic edema leading to neuronal degeneration [7, 8].

### c. Haematogenous spread

This route of entry of the virus has also been postulated, but detailed work in this regard is awaited.

### d. Immune system mediated injury

Cytokine storm, which is a well-known immune reaction of this particular viral infection, may lead to inflammation and injury of the nervous system. This idea is further supported by the observation that interleukin (IL-6), a pro inflammatory cytokine which gets released in excess during the stages of viremia, is positively correlated with the severity of COVID-19 symptoms which is followed by activation of T lymphocytes, macrophages, endothelial cells, activation of coagulation factors and other complement cascades, Disseminated intravascular coagulation (DIC) and lastly end organ damage [9, 10, 11].

## 3. Neurological Presentations

One interesting retrospective study reported that those presented with severe neurological manifestations had less typical constitutional symptoms of cough, fever etc [12]. But further research is necessary in this regard to arrive at a conclusion.

Off late, it came to the understanding that, COVID-19 can affect the central and peripheral nervous systems as well as the musculoskeletal system with various modes of presentations.

### a. Central nervous system presentations

#### 1. Dizziness

Though dizziness can be a prodrome to many disease entities. It has been also found in patients having Covid-19 in 16.8 % (p value-0.42) where it was more prevalent in severely affected individuals.<sup>10</sup> Some other studies stated it to be around 9% [12].

#### 2. Headache

Headache is also present in 13.1% (p value-0.15) and also present more frequently in severely affected individuals [13, 14]. Some other similar studies reported 6%-8% [12, 17, 18].

#### 3. Impaired consciousness and confusion

It was observed to be around in 8-9% individuals in several studies.<sup>16,20</sup> Some studies reported to be in around 65% in patients with neurological symptoms [13].

#### 4. Ataxia

In one study, ataxia was observed in one patient among 214 patients (0.5%) [12, 14].

#### 5. Seizure

Several case reports showed it can cause focal status epilepticus, generalized seizures or myoclonic seizures [12, 14, 15].

#### 6. Encephalopathy and Encephalitis

The causative factors for encephalopathy in Covid -19 patients are obscure. But it has found in patients having associated pre morbid conditions like previous stroke, neurodegenerative disorders, preexisting cardiac ailments or preexisting chronic obstructive airway diseases.

The possible causative factor for encephalopathy is thought to be hypoxia in the majority [12, 14, 19].

Studies reported the occurrence of encephalopathy to be in the range of 17.6% -40% [14, 20].

Till now, only one case of acute haemorrhagic necrotizing encephalopathy was reported. They had reported haemorrhagic rim enhancing lesions in bilateral thalami, medial temporal lobes and subinsular regions in MRI (Magnetic resonance imaging) brain imaging. The possible mechanism is thought not to be due to direct viral entry or to be due to cytokine mediated, associated with increased permeability of the blood brain barrier [21].

Cerebrospinal fluid analysis for Covid-19 confirmed encephalitis patient was also reported in one study. In that particular study, it was shown that there was involvement of the mesial temporal lobe as well as the hippocampus in MRI brain imaging [22].

## 7. Stroke

Both Ischaemic and haemorrhagic strokes have been reported in patients with COVID-19 infection. The investigating authors postulated that there may be dysregulation in ACE receptors leading to dysregulation of cerebral auto regulation, sympathetic-adrenal system, alteration of cerebral blood flow, possible blood pressure fluctuation, leading to cerebral haemorrhage (0.5%) [2, 11]. On the other hand, activation of endothelial and mononuclear cells leading to increased thrombogenesis resulting in free thrombi in circulation, alteration in coagulation cascade with consequent ischaemic stroke (5%) [2, 12, 14, 23].

Cerebral venous and arterial thromboembolism (0.5%) was also reported and can also occur with the same mechanism due to alteration in the coagulation cascade with a possibility due to the occurrence of hypercoagulable state [1].

## 8. Spinal cord involvement

Acute myelitis with paraplegia had also been reported in a case report due to COVID-19. The authors attributed acute myelitis due to the cytokine storm and over activation of the inflammatory response as evident by high levels of serum ferritin, C-reactive protein, Serum Amyloid-A and serum Interleukin-6 levels [24].

### b. Peripheral nervous system presentations

#### (i). Guillain Barre syndrome (GBS) like presentation

Several cases of GBS or GBS like illnesses were reported from across the globe both with typical or atypical presentations of GBS symptoms. They presented with in accordance with the classified different variant presentations like -pure demyelinating form, pure axonal form and axonal sensory motor form which were evident in nerve conduction studies [25, 26, 27, 28].

#### (ii). Anosmia

It has been observed in several studies (range=5.1%-68%) [12, 14, 29].

#### (iii). Hypogeusia

It was also observed in several studies as well (range=5.6%-17%) [12, 14, 29].

### (c) Musculo-skeletal system involvement

Myalgia, myositis with elevated serum creatinine

phosphokinase and lactate dehydrogenase levels have also been observed in several studies (range=10.7%-19.3%)<sup>[12, 14]</sup>.

The investigating authors postulated that it may be due to the direct viral effect on myocytes or immune mediated muscle injury<sup>[11]</sup>.

#### 4. Discussion & Conclusions

COVID-19 is of critical concern in the health care system not only for its rapid spread, potentiality in causing the collapse of the health care system, but also for its variability of presentation. Since some patients with COVID-19 remains asymptomatic initially clinically, so the diagnosis is a challenging one.

Thus, it poses an unique challenge to the Neurologist as well to the treating physician alike due to its varied clinical presentations, from respiratory to neurological manifestations. A sensitive data collection and meticulous documentation of clinical presentations are essential for a better understanding of its course. A high index of suspicion is also the key in preventing its spread to the health care providers as well to the community at large.

With the advancement of time, probably we will be able to unravel the mystery associated with this previously relatively unknown virus and the symptomatology it produces in humans.

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