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***Syed Zahid Ali***
*Medical Officer, Nishtar Medical University, Multan, Punjab, Pakistan*

***Saad Farooq***
*Nishtar Medical University, Multan, Punjab, Pakistan*

***Qurat Ul Ane Gillani***
*Assistant Professor, Institute of Molecular Biology and Biotechnology (IMBB), University in Lahore, Lahore, Punjab, Pakistan*

***Roy Arslan Ahmed***
*Medical Officer, Nishtar Medical University Multan, Multan, Punjab, Pakistan*

***Syed Muzaffar Hussain***
*PhD. Candidate (Psychology), School of Applied Psychology, Social Work & Policy (SAPSP), Universiti Utara Malaysia, Kedah, Malaysia*

***Saif ur Rasool***
*Department of Pediatrics Surgery, Children Hospital and Institute of Child Health Multan, Multan, Punjab, Pakistan*

***Shehna Farooq***
*Department of Chemistry, University of Wah, Rawalpindi, Punjab, Pakistan*

***Sami Ur Rahman***
*National Centre of Excellence in Physical Chemistry, University of Peshawar, Peshawar, Khyber Pakhtunkhwa, Pakistan*

**Correspondence:**
***1. Dr. Syed Zahid Ali***
Medical Officer, Nishtar Medical University, Multan, Punjab, Pakistan
Email: zaidi.prodigy@gmail.com

***2. Dr. Qurat Ul Ane Gillani***
Assistant Professor, Institute of Molecular Biology and Biotechnology (IMBB), University in Lahore, Lahore, Punjab, Pakistan
Email: quratulane.gillani@imbb.uol.edu.pk

# Possible mechanisms involved in neurological manifestation of COVID-19: A short review

*Syed Zahid Ali, Saad Farooq, Qurat Ul Ane Gillani, Roy Arslan Ahmed, Syed Muzaffar Hussain, Saif ur Rasool, Shehna Farooq, Sami Ur Rahman*

## Abstract

COVID-19 resulted in a pandemic causing respiratory infection due to the SARS-CoV-2 virus. It started from the Wuhan city of China in mid-December 2019 and then spread all over the world in a very short time. COVID-19 is mainly responsible for acute respiratory syndrome however, there are reports of involvement of some neurological symptoms and conditions wise; headache, dizziness, fatigue, insomnia, confusion and myalgia, encephalitis etc. The severe neurological effects consist of acute ischemic stroke, cerebral hemorrhage, cerebral venous sinus thrombosis, subarachnoid hemorrhage, acute necrotizing hemorrhagic encephalopathy, meningitis/encephalitis, and acute Guillain-Barre Syndrome. Neurological conditions could be due to the entrance of the virus into the brain via nasal passage through the olfactory bulb or the initiation of a storm of cytokines that cross the blood-brain barrier (BBB). It can also have a long-term effect in the form of demyelination of neurons which can lead to neurodegenerative diseases. This review deals with the general mechanisms which might be involved in the entrance of COVID-19 into the brain and its possible effects.

**Keywords:** SARS-CoV-2, Mechanisms, COVID-19, Neurological Manifestation, Possible Mechanisms, Case Studies.

## INTRODUCTION

The pandemic term is used when one particular disease spreads throughout the world causing serious life threats. In the 21st century, where we have high technology and advancement in medical sciences the world faced the first pandemic caused by SARS-CoV which started in Guangdong Province, China in 2002 and then spread to 37 countries with 8096 cases and 774 deaths. After a decade the MERS-CoV infected 2494 people over 27 countries with 858 deaths [1]. At the end of 2019 December, the world faced its worst and fastest pandemic with SARS-CoV-2 or later on termed as COVID-19 which originated in Wuhan, Hubei Province, China [2]. After the appearance of the first report from China on 30 January 2020 WHO announced it as public health emergency of international concern and on 11 February, 2020 coined the term Covid-19 [3]. The spread of Covid-19 was very fast and took only 30 days to spread the disease throughout the entire country [4]. WHO changed its status to a CoV epidemic outbreak very high level on 28 February [5]. After that, it spread to several other countries like Japan, Russia, Hong Kong, Italy, Iran, Pakistan, India and the United States [6]. In the last year 2020 data shared by WHO showed that a total of 216 were countries affected with 14.04 million confirmed cases with a total of 5.97 million deaths [7]. In Pakistan we have 1,212,809 confirmed active cases of which 5,122 are critical cases with 26,938 total deaths. Area wise most affected areas are Sindh (446,840), Punjab (416,901), KP (169,429), Islamabad (103,293), Balochistan (32,658) and AJK/GB (33,490 / 10,198) till 15, September 2021 [8].

It is observed that approximately one-third of the COVID-19 patients exhibit one neurological symptom and the most common are dizziness, headache, fatigue, and myalgia [9]. Acute ischemic stroke, cerebral hemorrhage, cerebral venous sinus thrombosis, subarachnoid hemorrhage, acute necrotizing hemorrhagic encephalopathy, meningitis/encephalitis, and acute Guillain-Barre Syndrome are some of the neurological complications reported with COVID-19 [10,11]. This review is aimed at the study of Covid-19 infection and its neurological manifestation. Before starting the neurological effect, we will discuss what COVID-19 is, from which family it belongs and how it is spread and what are general effects of COVID-19 are.

**Classification, Structure and life cycle of SARS-CoV-2**

CoVs have been isolated from both humans and animals (birds, pangolin, camels etc) and their zoonotic potential cannot be denied (Shereen et al. 2020). The CoV was first reported from an embryonic culture of the respiratory tract of a patient by Tyrrell and Bynoe and a child in 1960 and 1965 respectively [12]. The virus was named CoVs based on specific spike surface proteins. The CoVs are later on classified into four genera [6]. Birds and mammals are both infected by CoVs but this virus also can jump into humans [13]. CoVs variants for humans mostly belong to α and β coronavirus [14].

They are enveloped RNA (positive-stranded) virus having large genomes and are susceptible to change and mutations that results in the emergence of new viruses [15,16]. SARS-CoV-2 is a member of the β-coronavirus cluster which circulates in reservoirs of mammals and aves [3]. After sequencing the virus genome scientists believed that bat (*Rhinolophus affinis*) was the original host which jumped to humans with the help of an intermediate host of unknown origin [12].

SARS-CoV-2 has a round or elliptic shape with a diameter around 60-140 nm [5]. Under the electron microscope, the characteristics of a crown-like shape are due to a spike on a membrane made of glycoprotein [17]. The major viral protein in the envelope is (S) spike protein which facilitates entry of the virus to the host and determines the potential host cell and causes pathogenesis. The other proteins are (M) membrane protein, (E) envelope protein, and (N) nucleoprotein [18,19]. (N) Proteins are important for the incorporation of the RNA into the viral progeny and part of the replication/transcriptions complexes (RTCs) [20]. (HE) Hemagglutinin esterase is another important protein on Covid-19 containing acetyl esterase which binds sialic acids on surface glycoproteins [21]. As mentioned above that spike protein is primarily attached to hosts and in the case of SARS-CoV-2, they are attached with angiotensin-converting enzyme 2 (ACE 2) receptors of the hosts [19]. ACE-2 is a multi-specific enzyme and is present on the surface of the lung alveolar epithelial cells [22].

Other organs like the heart, kidney, peripheral and central nervous system also have ACE 2 receptors [1]. The life cycle of the virus initiates by conformational changes in S protein following attachment resulting in fusion of viral and host cell membrane that helps in releasing viral RNA into the host cell. Afterwards, that RNA genome translates (ORF1a and ORF1b) two large open reading frames and produces viral polyproteins "pp1a" and "pp1ab" which are cleaved by viral proteinases into small proteins [23]. These cleaved proteins modify into nonstructural proteins (nsps) and form replication/transcription complex. These complexes form viral replication organelles to provide a protective environment for the replication and transcription process [20]. This results in the production of subgenomic mRNA and then original viral proteins. RNA synthesis occurs in the cytoplasm. Protein synthesis takes place in the endoplasmic reticulum and post-translational modification occurs in the Golgi apparatus. After post-translational modification assembly of viral proteins with genomic RNA occurs after which viral particles are released from the cell eventually [23].

**Mode of transmission and clinical manifestation**

Three major modes of transmission of SARS-CoV-2 are droplets, respiratory secretions and direct contact [6]. The fecal swab studied from pneumonia patients also indicates the presence of SARS-CoV-2. After the transmission, the virus has an incubation period of around 2- 14 days [12]. One patient can infect approximately 1.4 - 2.5 persons [24]. Elder persons with medical complications like hypertension, diabetes, cardiac diseases specifically and using drugs that increase angiotensin-converting enzyme 2 (ACE-2) have high susceptibility [25]. The major symptoms that appear after 2-14 days post-exposure to COVID-19 include sore throat, cough, shortness of breath, fever and chills, fatigue, sputum production, myalgia and headache. Some people also exhibit diarrhea, runny nose, and vomiting [5]. The majority of CoV patients present mild to moderate illness and recover without any specific treatments [26]. The severe cases particularly immunocompromised patients have a high risk to develop intensive respiratory syndromes like acute respiratory distress syndrome (ARDS) and pneumonia. The major effects of Covid-19 are a decrease in WBC counts and lymphocytopenia. D-dimer, neutrophil count, blood urea, and creatinine levels increase with a simultaneous increase in inflammatory mediators like IL6, IL 10, IL 2, IL 7 [12]. Rismanbaf and Zarei reported increased acute renal injury along with inflammation of the kidneys [27]. The infection varies from asymptomatic to clinical conditions with the requirements of mechanical ventilation and ICU admission with multiple organ failure and death [5].

**The mechanism involved in Neurological manifestations of SARS-CoV-2**

Li et al. (2020b) thought that observations about COVID-19 involvement in the CNS and its effect on neurological complications are scarce and of low quality. Pathogenesis of neurological complications is complex and less documented It may be a cause of direct viral injury or indirect injury of neurons by Covid (Wu et al. 2020). The SARS-CoV-2 can take different pathways to reach the brain.

The direct injury to neurons could be a manifestation of the entry of virus in nerve cells as Li et al. (2020a) reported the attachment of Covid to lungs ACE 2 receptors or nasal passage to olfactory bulb reaching brain stem and affecting cardiorespiratory centre severely [28]. From the periphery, the SARS-CoV-2 can pass to the CNS using retrograde neuronal transport and synaptic connections via vagal nerve afferents from the lung [29].

The loss of sense of smell and taste has been considered a major diagnostic feature of Covid [30]. In the nasal passage, Covid may damage the olfactory nerve terminals causing loss of the sense of smell and a cribriform plate of the ethmoid bone in proximity to the olfactory bulb which can exhibit by loss of smell and taste [31]. The ACE 2 receptors are also present in the brain especially in different regions of the brain stem and are expressed in neurons as well as astroglial cells which play important role in neurological conditions [32]. The virus is released from the lungs and is transported to the central nervous system via the peripheral nervous system [33,34]. The brain stem has medulla oblongata and pons which contain the cardiorespiratory centre of the brain with a higher number of ACE 2 receptors [32].

Indirect effects of Covid-19 on CNS may be due to the development of the "Cytokine storm". The progression of disease increases the production of cytokines, chemokines, interleukins, and inflammatory signals which stimulate $CD4^+$ T-cells. $CD4^+$ T cells then produce granulocyte-macrophage colony-stimulating factor and induce macrophage lines to secrete interleukin-6 (IL-6) which can break Blood-Brain-Barriers (BBB) [35,36]. When BBB disrupts it intensifies the neuroinflammatory process which eventually causes functional brain damages [37].

The other factors which damage the neurons are the hypoxia caused by acute respiratory syndrome [38]. Minute changes in oxygen levels can cause irreversible damage to sensitive nerve cells or neurons resulting in temporary dysfunction and cerebral infarction. Abnormal events cascade starts due to failure of oxygen delivery to the brain. Brain injury results due to neuronal cell death via apoptosis induced by prolonged hypoxia.

Some non-specific neurological symptoms are also observed such as confusion and headache. Some COVID-19 patients exhibit more specific neurological conditions like seizures or cerebrovascular problems [39]. Possible pathogenesis of the COVID- 19 is shown by Wu et al. [40]. SARS-CoV-2 can also enter the nervous system via circumventricular organs which lack BBB and through dorsal root ganglia and autonomic ganglia which don't have BNB (blood-nerve-barrier) [41,42]. Bonetti worked with SARS-CoV-2 and reported that it infects endothelial cells, so systemic vascular endothelitis started vasoconstriction, edema and a procoagulant state which can cause cardiovascular stoke [43]. This vascular endothelium dysfunction also increases inflammatory response which is associated with tissue edema and pro-thrombotic state [44].

**Neurological complications of COVID-19**

Chen and his colleagues described that under chronic conditions cardiovascular along with cerebrovascular diseases were the most pervasive (40%) [1]. One patient suffered from acute hemorrhagic encephalopathy [45] and another patient with meningoencephalitis tested positive with a CoV [11]. Patient observation from Morocco hospital suggested that SARS-CoV-2 was responsible for central nervous system damage causing meningoencephalitis [46] and similarly cerebral venous thrombosis was observed in a patient of COVID 19 in France [47]. Bernard et al. reported two COVID-19 positive female patients also developed meningoencephalitis, severe neuropsychological symptoms and status epilepticus. Sometimes COVID-19 is not detected in RT-PCR but can be detected via imaging techniques and cerebrospinal fluid (CSF) test [48]. Moriguchi et al. described transient generalized seizure in the patient [11]. The RT-PCR was negative but the test with CSF was positive. MRI of the patient demonstrated abnormal observations of the medial temporal lobe including hippocampus which suggest encephalitis, post convulsive encephalitis, or hippocampal sclerosis. Haddadi et al. also reported the patient with encephalopathy tested positive for COVID-19 after the detailed examination [49]. Dr. Liu Jingyuan reported a case of a patient suffering from coronary pneumonia infected with SARS-CoV-2 confirmed by genetic sequencing in the cerebrospinal fluid.

The patient exhibited symptoms of brain injury, but a CT scan of the head did not record any abnormalities, and the CSF biochemical test was normal. A diagnostic test on the CSF of the patient was positive for SARS-CoV-2, so the patient was treated for viral encephalitis [50]. Similarly patients with positive COVID-19 presented with manifestations of pulmonary disease, convulsions along with altered mental status and confusion [51].

**Long term effects of COVID-19**

As long-term studies may reveal an increased risk of neuroinflammatory and neurodegenerative diseases, therefore, monitoring of acute neurological conditions of COVID-19 is recommended [35]. There is no observation for people who have recovered from severe COVID-19, they might be suffering from other symptoms which are not clinically evident [52]. It is stated by some scientists that SARS-CoV-2 infection increased the risk of schizophrenia in older adults [53]. Olfactory deficiency is also a characteristic of other virus's infections [54] and is also associated with neurodegenerative diseases like Alzheimer and Parkinson's disease. The patients of Covid-19 should be carefully monitored periodically after the recovery for the late neurological effects like neurodegeneration and demyelination which can cause diseases like Parkinson's disease and multiple sclerosis [55].

**CONCLUSION**

COVID-19 the pandemic that started in December 2019 created chaos all over the world and most of the countries were affected by it. It is spread by SARS-CoV-2 via attachment to ACE 2 receptors, especially in the lungs. Clinical manifestations concerned for COVID-19 consist of mild, moderate and severe. The common symptoms in mild to moderate cases comprise dry cough, headache, fever; shortness of breath but severe cases often result in acute respiratory distress syndrome, pneumonia and multi-organ failure. The neurological manifestations are although rare but have been observed in different cases. People do recover from COVID-19 hut the main consideration is long term neurological and non-neurological sequelae which can occur after the recovery phase. The main mechanism through which this virus enters the brain and causes damage is still not well known. The major information was collected and concluded by various case studies published in different articles.

**Conflict of Interest**

None declared.

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