

## The Control and Treatment of Neurological Complications in COVID-19 Pandemic Era

Hyunjo Kim<sup>1\*</sup> and Jae-Hoon Song<sup>2</sup>

<sup>1</sup>*School of Pharmacy, Yonsei University, South Korea*

<sup>2</sup>*Chairman of Asian-Pacific Research Foundation for Infectious and ANSORP, South Korea*

**\*Corresponding Author:** Hyunjo Kim, School of Pharmacy, Yonsei University, Incheon City, South Korea.

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### Abstract

The novel coronavirus (COVID-19) is a family of large enveloped non-segmented positive-sense RNA viruses which has been considered as a global health concern. COVID-19 itself has been a very high transmissibility potential, which declared as pandemic by WHO. It is postulated that the COVID-19 accumulates mainly in the nasal epithelia and lower respiratory airways. However, there is evidence suggesting the COVID-19 neurotropism which might contribute to respiratory failure. The magnitude of the COVID-19 pandemic will result in substantial neurological disease, whether through direct infection, para-infectious complications, or critical illness more generally. Thus, we aim to review the central nervous system complications of the COVID-19 and how to control and treat since the emergence of the virus in this study.

**Keywords:** Novel Coronavirus; COVID-19; CNS Complication; Neuropathy; Autoimmune System; CNS Disorder Treatment

### Abbreviations

SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; COVID-19: Coronavirus Disease 2019; ICU: Intensive Care Unit; ECMO: Extracorporeal Membrane Oxygenation; ACE2: Angiotensin Converting Enzyme 2; CNS: Central Nervous System; MV: Measles Virus; HIV: Human Immunodeficiency Virus; hRSV: Human Respiratory Syncytial Virus; IV: Influenza Virus; CoV: Coronavirus; hMPV: Human Meta-Pneumonia Virus; CSF: Cerebrospinal Fluid; MRI: Magnetic Resonance Imaging; BBB: Blood-Brain-Barrier; MS: Multiple Sclerosis; SR: Self-Reactive; ARDS: Acute Respiratory Distress Syndrome; IVIg: Intravenous Immunoglobulins; PLEX: Plasma Exchange; T2/FLAIR: T2-Weighted-Fluid-Attenuated

### Introduction

Coronaviruses are large enveloped non-segmented positive-sense RNA viruses, generally cause enteric and respiratory diseases in animals and humans [1-4]. Most human coronaviruses, such as hCoV-229E, OC43, NL63, and HKU1 cause mild respiratory diseases [5,6], but the worldwide spread of two previously unrecognized coronaviruses, the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have called global attention to the lethal potential of human Coronaviruses [7-9]. While MERS is still not eliminated from the world, another highly pathogenic coronavirus, currently named SARS-CoV-2 (previously known as 2019-nCoV), emerged in December 2019 in Wuhan, China. This novel coronavirus has caused a national outbreak of severe pneumonia (coronavirus disease 2019 [COVID-19 by WHO]) in China, and rapidly spreads around the world [10,11]. This virus shares highly homological sequence with SARS, and causes acute, highly lethal pneumonia coronavirus disease 2019 (COVID-19) with clinical symptoms similar to those

reported for SARS and MERS [12]. The symptom of COVID-19 is acute or chronic respiratory distress, and the characteristic of intensive care unit (ICU) patients could not breathe spontaneously without ventilator and extracorporeal membrane oxygenation (ECMO) machine. Furthermore, some of COVID-19 patients presented that mild signs such as headache, nausea, and vomiting bother their routine life. The neurological symptoms often originate in the peripheral nervous system and include burning, numbness, pins-and-needles (prickling) sensations, muscle weakness or paralysis, and sensitivity. Based on the above described evidences we can explain that COVID-19 may also invade the central nervous system (CNS) and it causes neurological complications [1,13,14]. As has been known about SARS infections in the CNS from both human and zoonotic sources, the stem cell of brain was lethally damaged. Additionally, some coronaviruses have capability of rapid spread to the medullary cardiorespiratory center via a synapse-connected route, which have been demonstrated the mechanoreceptors and chemoreceptors may play important role in the lung and lower respiratory airways. Considering the high similarity between SARS and COVID-19, it remains to make clear whether the potential invasion of COVID-19 is partially responsible for the acute respiratory failure of patients with them. The COVID-19-induced respiratory failure should be taken into account to perform guiding the significance for the prevention and treatment. On the purpose of discovering the neural virulence of COVID-19 the neurological tissue expression of angiotensin converting enzyme 2 (ACE2) has been introduced and referred from human protein databases [15-17]. It has been reported that ACE2 expression in the brain prompted us to investigate neurotropic effects of COVID-19 evidences based on literature and mammalian tissue expression databases. It will contribute toward the morbidity and mortality of COVID-19 patients for the pandemic perspective. Thus, COVID-19 is a rampant pandemic characterized predominantly by SARS-like syndrome. Coronaviruses cause direct central nervous system (CNS) infection and presumed para-infectious disorders as well [18-20]. While an exclusive evidence is sparse, over five million cases of confirmed COVID-19 have been listed in COVID-19 Pandemic Wikipedia and it is including worldwide 230 countries approximately at the date of May 21<sup>st</sup> 2020, therefore, emerging PubMed and Cochrane Library articles have been used for the neurological complications with COVID-19 infection. At this point of view, we provide a brief outline of the currently known neurological manifestations of COVID-19 and discuss some probable ways to design therapeutic strategies to overcome the executive global pandemic crisis throughout systemically reviewing.

### Cerebral involvement in the COVID-19 infections

One of the highest rate diseases in modern public health is central nervous system (CNS) infections as frequently COVID-19 patients demonstrate, which have long-term effects and can lead to poor quality of life and a significant economic or social burden for families and communities. A various kinds of viruses can enter the CNS and reveal acute or chronic CNS problems in the way of diverse spectrum [21]. In add-on, CNS disorders are caused by many routes of viral entry and oxidative stress plays a critical role in the viral life cycle as well as the pathogenesis of viral induced diseases, therefore, viral tropism, and immune responses should be considered [22]. The immune responses influence on the spread of virus where directly injure or apotheosis not only restriction but also moderate or severe CNS pathologies. In order to diminish the burden of CNS viral infections with COVID-19 pandemic the therapeutic interventions are definitely required [23]. CNS pathologies are originated from measles virus (MV) [24], herpes virus [25] and human immunodeficiency virus (HIV) [26], the human respiratory syncytial virus (hRSV), the influenza virus (IV), the coronavirus (CoV) and the human meta-pneumonia virus (hMPV) [27,28]. The clinical manifestations of CNS disorders induced by virus are febrile or afebrile seizures, status epileptics, encephalopathies and encephalitis as features mainly. It is suggested that all these viruses founded in cerebrospinal fluid (CSF) can spread rapidly throughout the CNS [29,30].

Firstly, we extracted conceptions from the most recent findings related to neurologic complications in this review article, secondly adjusting data such as the possible neural pathways and representative effects on the CNS, as schemed in figure 1.

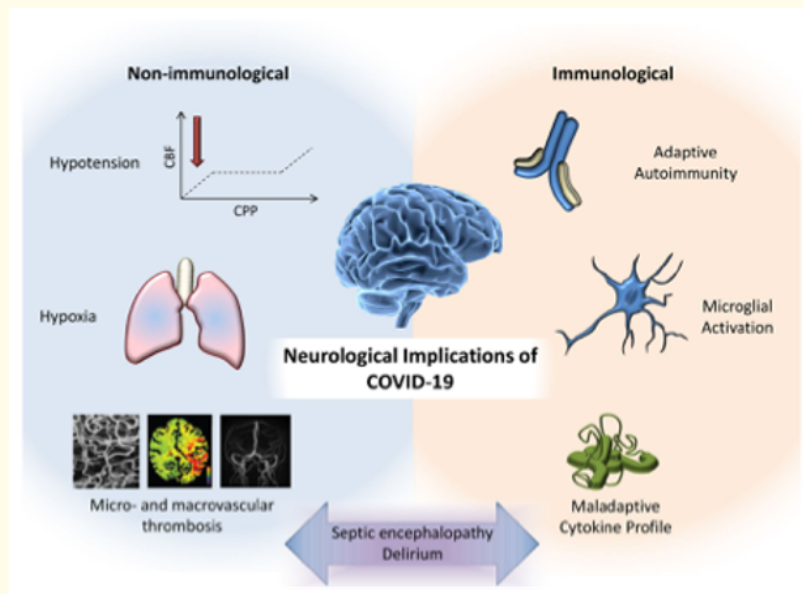


Figure 1: Putative mechanisms underlying neurological consequences of COVID-19.

The cerebral circulation enables CNS activity and also one of the factors for the COVID-19 infection related complications with ACE2 expression in the capillary endothelium. Additionally, the viral particles in the capillary endothelium damage brain stem and to initiate the viral access to the brain. Besides that, the observations from COVID-19 pandemic patients illustrated that impaired sense of smell/taste or hyposmia should be reconsidered for the purpose of cerebral involvement in neurological complications.

### COVID-19 infections affecting the CNS

A virus particle, also called a virion, consists of genes made from DNA or RNA which are surrounded by a protective coat of protein called a capsid where coronaviruses are 100 nm in size, spherical or oval as well as crown-like shape [5]. Viral infections in the CNS are well understood that neurotropic virus particles invade nervous tissues and neuron cells causing infectious diseases on immune-functioning macrophages. The potential nervous system damages [31-34] originated from COVID-19 infection and their managements are described below in table 1.

CNS disorder	Case study		
	Symptoms	Treatment	References
Viral meningitis	Headache, fever and a stiff neck.	Antiviral medication	High Throughput. 2018 Dec; 7(4): 32.
Anosmia	Nasal congestion	Antibiotics, antidepressant	Rev Med Suisse. 2020 Apr 29;16(N° 691-2):849-851.
Encephalitis	Aches in muscles or joints, Fatigue or weakness, Confusion, agitation or hallucinations, Seizures	Anti-inflammatory drugs, Acyclovir, Ganciclovir, Foscavir	Brain Behav Immun. 2020 Apr 10. pii: S0889-1591(20)30465-7

Postinfectious acute disseminated encephalomyelitis	Visual loss, seizures, paralysis, and difficulty coordinating voluntary muscle movements	Anti-inflammatory drugs, intravenous corticosteroids; methylprednisolone	Rev Neurol. 2020 May 1;70(9):311-322.
Postinfectious brainstem encephalitis	Confused thinking, seizures, or problems with movement or with senses such as sight or hearing.	Antiviral medications; Acyclovir, Ganciclovir, Foscavir	World Neurosurg. 2020 May 6. pii: S1878-8750(20)30932-3.
Guillain-Barré Syndrome	Prickling, pins and needles sensations in your fingers, toes, ankles or wrists	Immunoglobulin therapy	J Pak Med Assoc. 1997 May;47(5):145-7.
Myositis	Tripping and loss of balance	Certain immunosuppressants; omeprazole, adalimumab, copains	Ann Rheum Dis. 2020 Apr 23;annrheumdis-2020-217573.
Acute necrotizing hemorrhagic encephalopathy	Seizures, disturbance of consciousness, coma, liver problems, and neurological deficits	Steroid medications, intravenous immune globulin (IVIG), plasmapheresis, chemotherapy	Radiology. 2020 Mar 31:201187.

Table 1: Acute neurologic complications of coronavirus infections.

The mechanism of COVID-19 infection is assumed mainly throughout both blood circulation pathways and neuronal pathways such as hypoxia, immune injury, ACE2 [35] and other routes as schemed in figure 2. We must aware of neurological manifestations during COVID-19 pandemic period and predict unexpected neurological symptoms [36] with CT imaging and CSF analysis and magnetic resonance imaging (MRI [34]; described in last chapter).

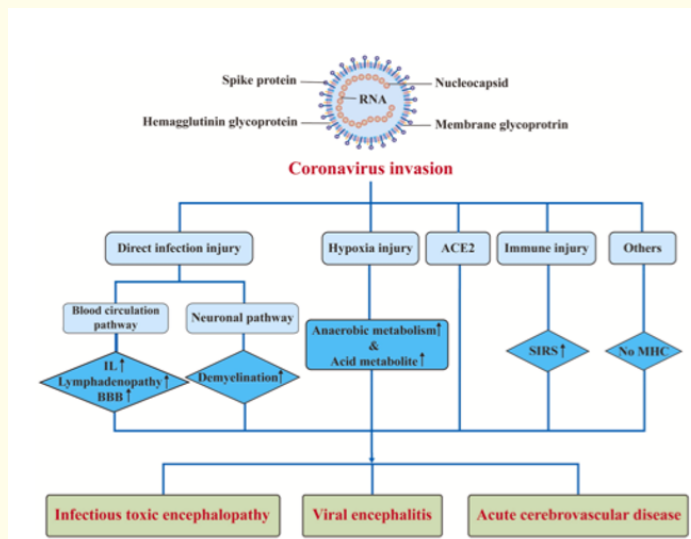
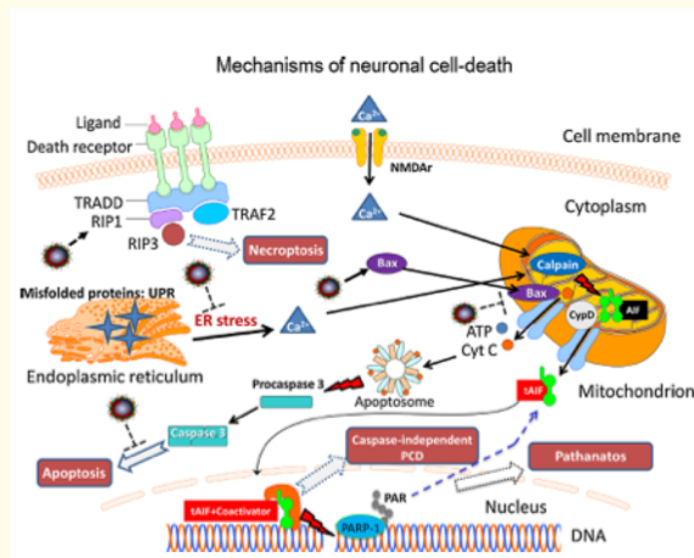


Figure 2: Pathogenesis of nervous system injury caused by coronaviruses. ACE2: Angiotensin-Converting Enzyme 2; BBB: Blood Brain Barrier; IL: Interleukin; MHC: Major Histocompatibility Complexes; SIRS: Systemic Inflammatory Response Syndrome.

On the other hand, the CNS may be para-infectious neurological diseases such as Guillain-Barré syndrome [37], transverse myelitis [38], or acute disseminated encephalomyelitis [34,39]. In the 2015-2016 Zika virus epidemic [40], it was narrowing scope only in South America region but COVID-19 pandemic is worldwide with the most great concern. COVID-19 infection patients have been reported with mild (anosmia and ageusia) to severe (encephalopathy) neurological manifestations, and if that is so, then it gives us more reasons to be frightened of this killer virus. Keeping in mind that the situation does not worsen from here, immediate awareness and more thorough research regarding the neural invasive nature of the virus is the immediate need of the hour. Scientists globally also need to up their game to design more specific therapeutic strategies with the available information to counteract the pandemic. We provide a brief outline of the currently known neurological manifestations of COVID-19 and some possible ways to design therapeutic strategies to overcome the present global pandemic outbreak, which are condensed in table 1. The coronavirus not only affect the respiratory system, but also have deleterious effects on the central nervous system. Most neurological diseases could be caused by coronavirus invasion. Coronaviruses cause nerve damage via diverse pathways which will be described below.

### Neuronal pathway

It is surely occurring to millions of people in cities across the country as the COVID-19 pandemic escalates with that the rapid spread of the disease has seen people fall ill. Likely, coronaviruses can make infection by the abnormal migration of neurons in the brain and nervous system. In the brain, neurons must migrate from the areas where they are born to the areas where they will settle into their proper neural circuits connected to neuronal transport through the motor proteins, dynein and kinesins [41,42]. For an instance, the COVID-19 can enter the brain through the olfactory tract as well as nasal route after COVID-19 infection and cause inflammation and demyelinating reaction [31]. Our observation of viral particles in endothelial cells may have implications for the route of entry for COVID-19 into the CNS. There are two pathways, the hematogenous and neuronal retrograde routes have been proposed for the entry of neurotropic respiratory viruses into CNS. Coronaviruses undergo to approach neuron cell bodies and endothelial cells of blood-brain-barrier (BBB), the epithelial cells of the blood-cerebrospinal fluid barrier (the choroid plexus) in the peripheral and/or CNS at the threshold route of retrograde and hematogenous respectively. The fact is that CNS disorders are the most essential factor although trans-neuronal route and mechanisms are not gained access to the CNS. The mechanisms of coronavirus interactions with the nervous system to design intervention strategies which may induce neuronal degeneration and could participate in the exacerbation of human neuronal pathologies (See figure 3) are appropriate in this review article.



**Figure 3:** Pathways of neuronal degeneration and programmed cell death (PCD) activated or potentially inhibited after COVID-19 infection of neuronal cells.

**CNS consequences of COVID-19 possibility for long term period**

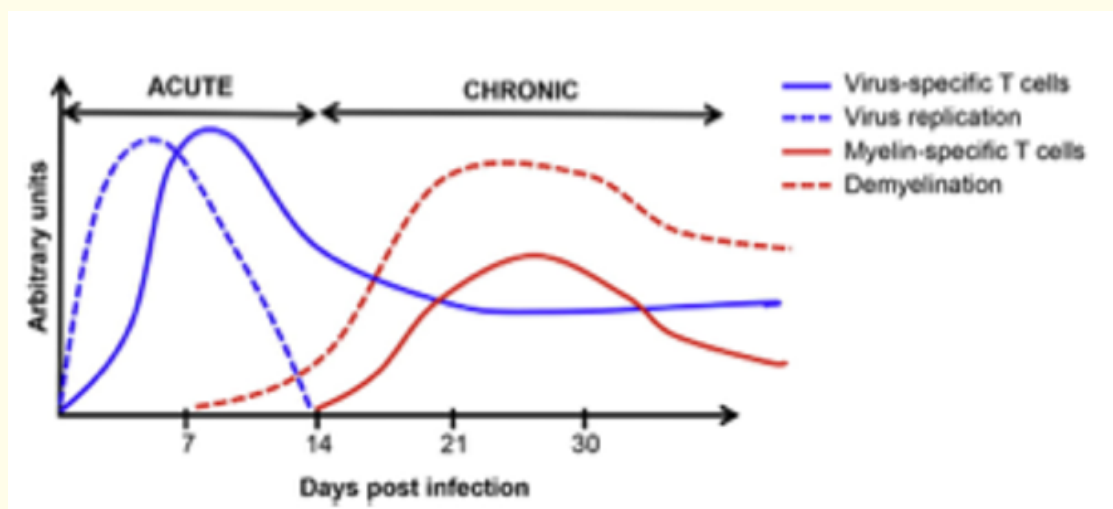
The neurodegenerative diseases such as Parkinson’s Disease (PD) and Alzheimer’s Disease (AD) are a gradual process and COVID-19 pandemic will be spread gradually. Therefore, the severity of the disease will be leveraged for the possibility of COVID-19 affecting the CNS. The earlier diagnosis stages of neurodegenerative disorders such as PD and AD is the most urgent weighting factor. Additionally, the above mentioned neurodegenerative diseases and the CNS complications induced by COVID-19 are struggling neuronal cell damages via impaired Blood-Brain Barrier (BBB) function, further contribute to neurological syndromes [34,43]. The COVID-19 pandemic will be continued to neurodegenerative disorders as infected individuals are increasing.

In neurological complication points of view, we expect the potential long-term CNS consequences of COVID-19 possibility based on the current pandemic and the high transmissibility of COVID-1.

Furthermore, infections as genetic and environmental factors have been proposed to contribute to disease induction and relapsing events in multiple sclerosis (MS) [44,45], an autoimmune demyelinating disease of the central nervous system (CNS). While research has mainly focused on virus associated autoimmune activation, less is known about prevention of autoimmunity, especially following resolving infections associated with CNS tissue damage. This review discusses novel insights on control of self-reactive (SR) T cells activated during neurotropic coronavirus- induced demyelination. A new concept is introduced that SR T cells can be dampened by distinct regulatory mechanisms in the periphery and the CNS, thereby preventing autoimmune disease for long-term possibility (See figure 4). The immune response may participate in the induction or exacerbation of neural pathologies such as MS in genetically or otherwise susceptible individuals (the reported data [46] was excerpted and summarized in table 2).

	Gender	COVID-19	229E	Both
Normal controls	Male	4 (19)	9 (19)	4 (19)
	Female	1 (5)	2 (5)	0 (5)
AD, PD, ALS and OND	Male	2 (13)	6 (13)	2 (13)
	Female	1 (13)	3 (13)	0 (13)
Multiple Sclerosis	Male	7 (20)	11 (20)	5 (20)
	Female	7 (9)	9 (9)	6 (9)

**Table 2:** Detection of viral RNA in brain samples and of cross-reactive T-cell clones between myelin and COVID-19 antigens in control and MS patients.



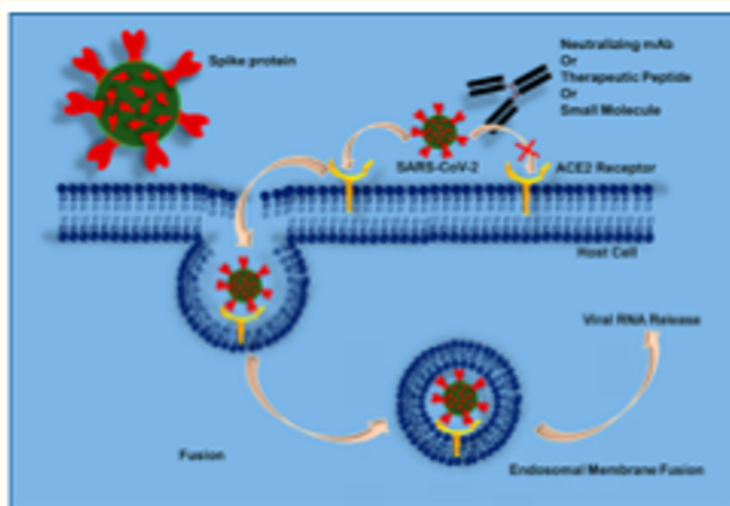
**Figure 4:** Kinetics of virus- and SR T cell responses during COVID-19 infection. CNS infiltration of virus-specific T cells is maximal and essential to control infectious virus. Anti- viral T cell effector function triggers demyelination.

**Controlling COVID-19 treatment strategy**

Central Nervous System (CNS) involvement can complicate infections both by viruses that primarily affect humans, and by some animal viruses that can cross species barriers to infect humans, particularly vulnerable populations. Notably, coronavirus have also shown neurotropic potential in a range of animal hosts as well as in humans. The neuronal invasive coronaviruses have been linked to encephalitis and paralytic poliomyelitis.

According to the proposed scheme in figure 5, potential strategy for therapeutic intervention is planned as following:

- Firstly, further considerations relate to patients with neurological conditions requiring treatments that could worsen outcome from COVID-19. Recent reports suggest some benefit in the most severe cases of COVID-19-related ARDS [31-34,47,48] may be prolonged in patients treated with corticosteroids and their routine use is currently avoided.
- Secondly, intravenous immunoglobulins (IVIg) or plasma exchange (PLEX), are less likely to delay viral clearance in COVID-19, and given some reports of benefit in sepsis, they may even be of potential benefit.
- Thirdly, neural inflammatory conditions such as cyclophosphamide or rituximab are likely to represent the highest risk treatments with regard to subsequent COVID-19 infection.
- Lastly it has been taken into account in depth for the chronic neurological consequences of COVID-19 pandemic in long-term cognitive impairment. In addition, we have to do planning for next generation coronaviruses with the new vaccine development.



**Figure 5:** A schematic representation of the route of COVID-19 infection and potential strategy for therapeutic intervention.

Hence, COVID-19 infection causes multiple organ damage including pulmonary, cardiovascular, renal, coagulation, gastrointestinal tract, and muscles. Our observation suggests that CNS may be another target of COVID-19 infection, and thus should be considered in any

patients with progressive or worsening CNS findings. As shown in figure 6, MRI identified multiple bilateral patchy areas of signal abnormality that appeared high on T2/ FLAIR images seen in the periventricular, deep white matter, subcortical area, corpus callosum, bilateral brachium points, midbrain as well as in the left cerebellum and upper cervical cord. The lesions were non-enhancing and showed diffusion restriction. The three patients presented with severe neurologic syndrome which included altered level of consciousness ranging from confusion to coma, ataxia, and focal motor deficit. Brain MRI [34] revealed striking changes characterized by widespread, bilateral hyperintense lesions on T2-weighted imaging within the white matter and subcortical areas of the frontal, temporal, and parietal lobes, the basal ganglia, and corpus callosum. None of the lesions showed gadolinium enhancement. Therefore, CNS involvement should be considered in patients with COVID-19 and progressive neurological disease, and further elucidation of the pathophysiology of this virus is needed.

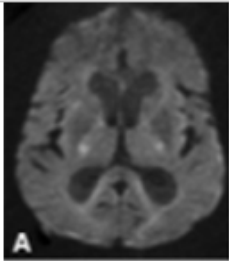

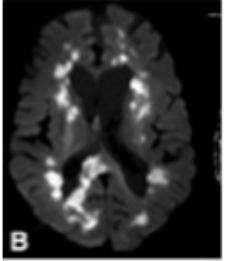

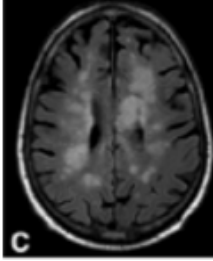
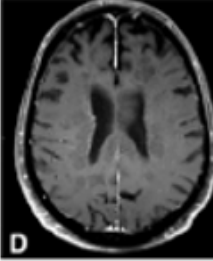
Hospital	Diffusion weighted imaging (DWI)	Apparent Diffusion Coefficient (ADC)	Axial fluid-attenuated inversion recovery (FLAIR) images	Axial contrast enhanced T1-weighted (T1WI)
Day 5				
Day 28				

Figure 6: Magnetic resonance imaging (MRI) of the chosen patient.

Discussion

Coronavirus disease 2019 (COVID-19) is a pandemic nominated by WHO but it has not been investigated much on neurological complications of COVID-19 infected patients. Encephalopathy [39] has not been described as a presenting symptom or complication of COVID-19 neither. Therefore, the neurological manifestations of COVID-19 must be included in future investigations as well as new vaccine discovery. Some patients without typical symptoms of COVID-19 came to the hospital with only neurological manifestation as their presenting symptoms. In some cases, these issues could be life-threatening: there were at least stroke or brain hemorrhage observed among those patients. In order to obtain deeper insights into the neural trajectory of COVID-19 infection. therapeutic interventions and strategy are needed to lessen this COVID-19 pandemic [49,50].



## Conclusion

Coronavirus infections can affect the nervous system through neuronal pathway and may lead to neurological diseases as well as CNS involved disorders. Therefore, patients with COVID-19 infections should be examined carefully via early diagnosis for neurological symptoms such as mild to severe cases among pathological signs. The COVID-19 infection-related neurological complications are key parameters to manage all patients. In this review article, we provided a brief outline of the currently known neurological manifestations of COVID-19 and discussed some probable ways to design therapeutic strategies to overcome the executive global pandemic crisis throughout systemically reviewing for further new vaccine development fundamentals eventually.

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## Conflict of Interest

All authors declare no competing interests. In compliance with the uniform disclosure form, all authors declare the following:

- **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.
- **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
- **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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