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Possible mechanism of central nervous system targeting and neurological symptoms of the new-coronavirus (COVID-19): literature review

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Abstract. **The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the 2019 Coronavirus Disease (COVID-19) has been associated with several neurological symptoms.**

This review aimed to highlight the possible mechanism of central nervous system (CNS) targeting and the neurological symptoms that may occur with the COVID-19 infection.

The case reports containing the keywords "neurological symptoms" and "COVID-19" were thoroughly reviewed to identify possible mechanisms of CNS targeting and neurological manifestations associated with COVID-19 infection.

The angiotensin-converting enzyme-2 (ACE2) receptors have been identified as the functional receptor for SARS-CoV-2. SARS-CoV-2 can affect the CNS through the following mechanisms: 1) Direct infection. 2) Blood pathway. 3) Neuronal pathway. 4) Immune-mediated injury/pathway (Cytokine Storm Syndrome).

COVID-19 virus, a neurotropic virus, was isolated from the cerebral fluid (CSF) and responsible for several neurological manifestations. The COVID-19 infection primarily affects CD4+ and CD8+ T-lymphocytes and it induces a surge of inflammatory cytokines, known as Cytokine Storm Syndrome (CSS). The Interlukine-6 (IL-6) is the primary CSS component. The IL-6, interferon-γ and endothelial growth factor were significantly higher in COVID-19 infected compared to non-infected individuals. The improvement of the COVID-19 patients after interleukin receptor blockers supports the CSS theory. The spectrum of SARS-CoV-2 neurological manifestations includes encephalitis, viral meningitis, post-COVID-19 infectious acute disseminated encephalitis, Guillain-Barré Syndrome (GBS), Miller-Fisher syndrome (MFS) and acute cerebrovascular disease (CVD).

Several COVID-19-associated neurological manifestations have been reported. Thus, it is important to identify and treat neurological symptoms as soon as possible to avoid long-term effects. The care providers should take the appropriate preventive precautions because patients can present with neurological manifestations of COVID-19 without any respiratory symptoms. Future research is warranted to confirm the relationship between SARS-CoV-2 and the development of neurological manifestations.

Key Words:
Central nervous system, Neurological symptoms, New coronavirus, COVID-19.

Introduction

The new public health COVID-19 pandemic is putting the entire globe in peril with the introduction of the novel coronavirus (2019n-CoV) or the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

The COVID-19 outbreak began in Wuhan (China) in December 2019 and expanded to other countries[1] and became a pandemic all over the entire world.

The reported symptoms were caused either by the viral infection itself or its repercussions. The COVID-19 individuals had a wide range

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of neurological manifestations (ranging from headaches to encephalitis)[2].

The coronaviruses are enveloped single-stranded RNA viruses, related to the coronaviradae family. Under an electron microscope, the tiny viral spikes (S) peplomers on the surface envelope give the virus its crown-like look. Bats are the primary reservoir for SARS-CoV-2 (a zoonotic origin). It spreads through droplet transmission, direct contact or contaminated stools[3].

Patients with severe COVID-19 exhibit greater neurological symptoms than those with mild infection, including acute cerebrovascular accidents, altered awareness and skeletal muscle injury[3].

Because of the common COVID-19 respiratory symptoms, which usually co-exist with the neurological manifestations. Li et al[4] proposed that, in addition to the direct lung injury, the SARS-CoV-2 produces a brain stem damage, which may play a role in the acute respiratory failure that affects the COVID-19-infected individuals.

The COVID-19 infection primarily affects CD4+ and CD8+ T-lymphocytes[5]. COVID-19 induces a surge of inflammatory cytokines from the glial cells, known as Cytokine Storm Syndrome (CSS)[6]. The interleukin-6 (IL-6) is the primary CSS component[7] (Figure 1).

The pro-inflammatory cytokines such as Interlukine-6 (IL-6), IL-2, IL-5, and tumor necrosis factors (TNF) were released from the activated glial cells in an *in-vitro* experiment[7].

Zendelovska et al[8] found the IL-6, interferon-γ, and endothelial growth factor (EGF) were significantly higher in COVID-19-infected compared to non-infected individuals. The improvement of COVID-19 patients after the IL-6 receptor blocker (tocilizumab) supports the COVID-19-associated CSS theory[9].

Additionally, Yildirim et al[10] found both anakinra and tocilizumab (IL receptor blockers), combined with the standard COVID-19 treatment, reduced the risk of intubation in COVID-19-severe pneumonia.

Therefore, this review highlights the possible mechanism of the central nervous system (CNS) targeting and the neurological symptoms that may occur with the COVID-19 infection.

Mechanism of CNS Targeting

The SARS-CoV-2 is a member of the coronavirus family. It is a single-stranded RNA virus, enveloped with a spiky glycoprotein membrane[11]. The main principal receptors for the SARS-CoV-2 are the angiotensin-converting enzyme-2 (ACE2) receptors[12] (Figure 1).

Both SARS-CoV and MERS-CoV viral nucleic acids were found in the cerebrospinal fluid (CSF) after a brain autopsy, which could explain the neurological manifestations caused by the coronavirus family[13].

The SARS-CoV-2 is a neurotropic virus that shares structural similarities with both the SARS-CoV and MERS-CoV and may utilize the same mechanism for the neurological manifestations[11].

The SARS-CoV-2 can affect the CNS through the following mechanisms: 1) Direct infection. 2) Blood pathway. 3) Neuronal pathway. 4) Immune-mediated injury/pathway.

Direct Infection

Entry of SARS-CoV-2 into brain tissues is expected to occur via the cribriform plate, which is located near the olfactory bulb[14] (Figure 2). The anosmia and hyposmia that occur with the SARS-CoV-2, may support the direct infection theory[2].

The ACE2 (the angiotensin-converting enzyme-2) receptors has been identified as the functional receptor for SARS-CoV-2[15]. The SARS-CoV-2 can attack the cerebral vasculature and neurons since both express ACE2 receptors[16].

A study[2] involving 214 patients, found that SARS-CoV-2 had neurotropic potential and reported neurological manifestations in 36.4% of the studied patients. The COVID-19 virus was isolated from the neuronal and vascular endothelium of the frontal cortex after a brain autopsy[17] (Figure 2).

Blood Pathway

The spikes on the glycoprotein envelope of COVID-19, enable the SARS-CoV-2 virus to bind to ACE2 receptors[18], and its binding affinity is 10-20 times greater than that of SARS-CoV-1[19].

The capillaries sluggish blood flow allows the viral spikes to interact with the ACE2 receptors[14]. Additionally, the viral interaction with the ACE2 receptors expressed over the neurons may cause neuronal damage without triggering a major inflammatory response or CSS[19].

Neuronal Pathway

Like coronaviruses, the neurotropic COVID-19 virus can invade the neurons through anterograde and retrograde movements across the sensory and motor nerve terminals[20] and through the vagus afferent nerve endings in the lungs (being a specific target)[4], (Figure 2).

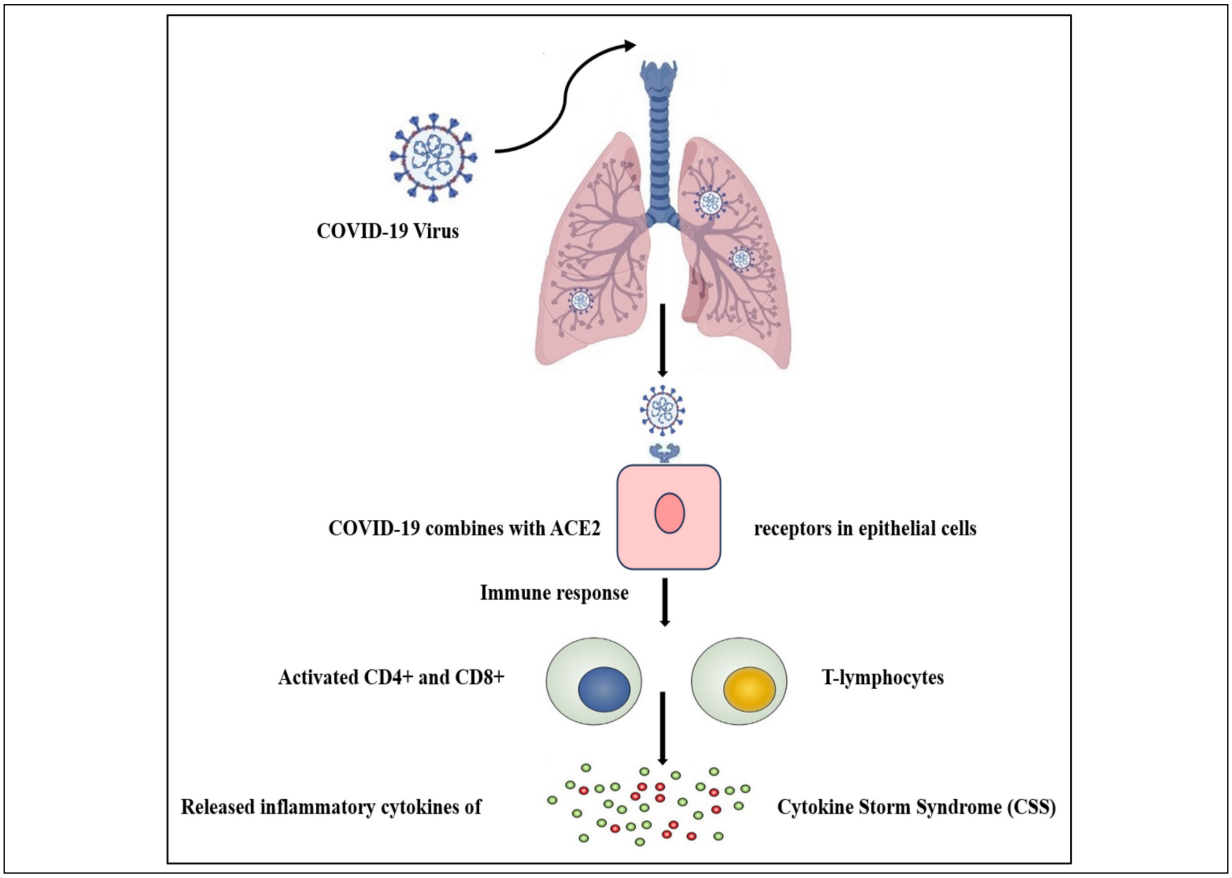

Figure 1. Sequence of inflammatory cytokines release in the cytokine storm syndrome (CSS).

Moreover, the sympathetic afferent and enteric nerves are entry routes for the SARS-CoV-2 into the gastrointestinal tract and CNS[21].

Immune-Mediated Injury/Pathway

The COVID-19 infection primarily affects CD4+ and CD8+ T-lymphocytes[5], and it induces a surge of inflammatory cytokines known as CSS[6]. Zendelovska et al[8] found that IL-6, interferon-γ and EGF were significantly higher in COVID-19 infected compared to non-infected individuals.

The improvement of COVID-19 patients after the IL-6 receptor blocker (tocilizumab) supports the COVID-19-associated CSS theory[9].

Additionally, Yildirim et al[10] found both anakinra and tocilizumab (IL receptor blockers), combined with the standard COVID-19 treatment, reduced the risk of intubation in COVID-19-severe pneumonia.

Moreover, a retrospective study[22] including 1,700 COVID-19 patients found that age, co-morbidities, immunological, radiographic, and laboratory abnormalities were collectively or individually predictors for poor outcomes after COVID-19 infection.

The SARS-COV-2 Neurological Manifestations Spectrum (Table I)

Encephalitis

Herpes simplex virus (HSV), varicella-zoster virus (VZV), influenza virus[23], and SARS-CoV[13] are the most common causes of viral encephalitis.

The SARS-CoV-2 can have neurotropic effects in addition to its typical respiratory symptoms[2]. Additionally, the SARS-CoV-2 genome sequence was isolated from the CSF of a Japanese patient who had clinically proven meningoencephalitis[24].

Poyiadji et al[25] reported a COVID-19 infection in a 50-year-old woman after three days of fever, coughing, and an impaired mental condition. Her CSF examination ruled out bacteria, HSV and VZV infection. A non-contrast brain computerized tomography (CT) scan showed a symmetrical bilateral thalamic hypoattenuation. The temporal and thalamic lobes on magnetic resonance imaging (MRI) showed acute necrotizing encephalitis[25].

Poyiadji et al[25] claimed that rather than directly invading the brain, the SARS-CoV-2 produces acute necrotizing encephalitis through the CSS.

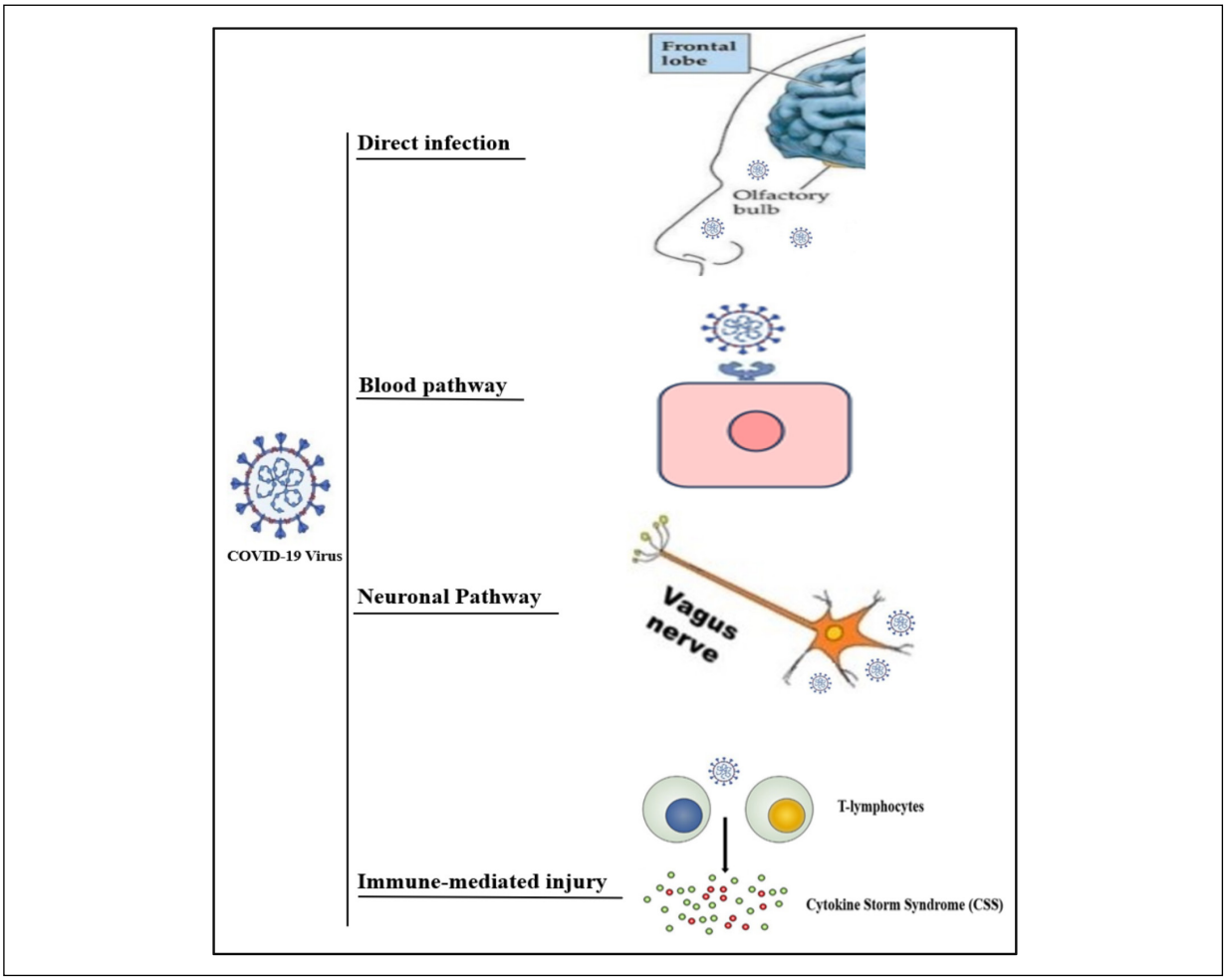

Figure 2. Mechanism of central nervous system (CNS) targeting in COVID-19 infection.

Table I. The reported neurological manifestations of COVID-19 in previous reports.

Manifestations	Authors (Type of study) - Presentations
Encephalitis	Moriguchi et al[24] (Case-report) - Headache, fatigue, and fever. Poyiadji et al[25] (Case-report) - Fever, cough and altered mental status.
Anosmia	Gane et al[26] (Case-report) - Hyposmia with headache and fatigue Eliezer et al[27] (Case-report) - Isolated anosmia Klopfenstein et al[28] (Retrospective) - Anosmia
Viral meningitis	Moriguchi et al[24] (Case-report) - Headache, fatigue, and fever. Duong et al[29] (Case-report) - Headache, fever, and seizure.
Guillain-Barré syndrome (BGS)	Zhao et al[30] (Correspondence) - Fatigue and leg weakness Toscano et al[31] (Case-series) - Lower limb paralysis - facial diplegia and ataxia. Sedaghat et al[32] (Case-report) - Quadriplegia after having cough and fever. Virani et al[33] (Case-report) - Bilateral numbness and weakness of lower limbs. Gutierrez-Ortizet et al[34] (Case-report) - Diplopia after having diarrhea and fever.
Acute disseminated post-infectious encephalitis	Arabi et al[35] (Retrospective) - Altered level of consciousness to coma and ataxia. Kim et al[36] (Case-series) - Numbness to ataxia and ophthalmoplegia.
Acute cerebrovascular disease	Mao et al[2] (Retrospective) - Ischemic stroke and hemorrhagic stroke. Oxley et al[37] (Correspondence) - Large-vessel stroke. Avula et al[38] (Case-series) - Computerized tomography proven stroke. Al Saiegh et al[39] (Case-report) - Subarachnoid hemorrhage and ischemic stroke

The CSS may be the cause of COVID-19's severe symptoms[40]. Severe COVID-19 is associated with elevated cytokines, including IL-1, IL-6, TNF, macrophage inflammatory protein-1, gamma-interferon, and granulocyte colony-stimulating factor[41].

The IL-1 (Anakinra)[42] and the IL-6 (Tocilizumab)[9] receptor blockers showed a significant improvement in COVID-19-infected individuals, which supports the COVID-19-associated CSS theory. Additionally, Yildirim et al[10] found both anakinra and tocilizumab, combined with the standard COVID-19 treatment, reduced the risk of intubation in COVID-19-severe pneumonia.

Anosmia

Loss of smell (anosmia) or a decreased sense of smell (hyposmia) are common symptoms/manifestations of COVID-19 infection and can be the only presenting symptoms in COVID-19-infected individuals[43].

Eliezer et al[27] also reported hyposmia and dry cough in a COVID-19-positive woman. Klopfenstein et al[28] retrospective study found 47% (54/114) of the COVID-19 infected individuals had anosmia. The anosmia usually starts 4.4 days (±1.9 SD) after the COVID-19 infection and persists for an average of 8.9 days (±6.3 SD).

Olfactory impairment was reported in 85.6% of the COVID-19 patients, and it was more common in females[44]. Anosmia is the most prevalent neurological manifestation of SARS-CoV-2[45], and patients with isolated anosmia should be screened for SARS-CoV-2 infection[46].

Viral Meningitis

There was a case of meningitis following SARS-CoV-2[24], reported in a Japanese patient with altered consciousness and an epileptic episode. Blood tests showed higher levels of leukocytes and C-reactive protein (CRP). He developed neck stiffness, and his right lung had ground glass opacity on CT, with no brain abnormalities[24].

Encephalitis and right lateral ventriculitis were diagnosed after the brain MRI. The CSF examination showed a positive COVID-19 polymerase chain reaction (PCR) test, although the nasopharyngeal PCR test for COVID-19 was negative.

He was given Laninamivir® (neuraminidase enzyme inhibitor) and antipyretic drugs for the fever, which started 9 days prior to admission. The authors concluded that a negative nasopharyngeal COVID-19 PCR test cannot rule out COVID-19 infection, and a positive CSF COVID-19 PCR explains COVID-19's neurotropic ability[24].

A 40-year-old diabetic woman developed seizures, stiff neck, and photophobia after an attack of headache and fever[39]. The blood chemistry, brain CT, liver and kidney function tests, and the chest X-ray were normal. She was diagnosed with viral meningitis and treated with ceftriaxone, vancomycin, and acyclovir[39]. The acyclovir was stopped when the PCR test for the HSV came back negative. Levetiracetam (anti-epileptic) was then given to stop her seizures. She was eventually given hydroxychloroquine after developing signs of confusion, agitation, and hallucinations. After the positive COVID-19 PCR test result, the authors concluded that COVID-19 can cause meningitis and can initially present with neurological symptoms[39].

Post-COVID-19 Infectious Acute Disseminated Encephalitis

Because of their neurotropic ability, the coronaviruses, have the potential to produce severe neurological manifestations such as acute disseminated post-infectious encephalitis and post-infectious brainstem encephalitis[47,48], especially in patients with autoimmune diseases such as multiple sclerosis or myasthenia gravis[23].

Guillain-Barré Syndrome (GBS)

Commonly, GBS occurs after gastrointestinal or respiratory tract infection caused by Campylobacter jejuni[49], Zika virus[50], or influenza virus[51].

The peripheral nerves in GBS are damaged by the COVID-19-associated immune injury/pathway[52].

A 61-year-old woman was admitted with significant fatigue, leg weakness, lymphocytopenia, and thrombocytopenia. She was diagnosed with GBS and was treated with intravenous immunoglobulins (IVIGs). She had abnormal laboratory findings, including lymphocytopenia and thrombocytopenia, and she developed a dry cough and fever (on the 8th day), and her oropharyngeal PCR test for COVID-19 came positive[53].

This case explains the para-infectious profile between the GBS and COVID-19, which is different than the conventional post-infectious profile seen between the GBS and Zika virus[50] or influenza virus[51].

Five individuals in Italy were diagnosed with GBS following COVID-19 infection[31]. Four patients originally presented with lower limb paralysis and paraesthesia, whereas one patient presented with facial diplegia and later developed ataxia and paraesthesia (3 of them were ventilated). There was a 5-10 days interval between the COVID-19 infection and the development

of GBS manifestations. The COVID-19 nasopharyngeal PCR test was positive in 4 of them. Four of them were treated with IVIGs, and one of them underwent a plasma exchange. One out of 5 was discharged walking after four weeks, 2 of them were receiving physiotherapy, and the remaining 2 were still ventilated[31].

A second incident of GBS being connected to COVID-19 has been reported in Iran[32] and describes a patient presented with quadriplegia two weeks prior to the onset of cough, fever, dyspnea, and positive COVID-19 nasopharyngeal PCR test. The patient had reduced fine touch sensation distal to the ankle, bifacial nerve palsy, and lost deep tendon reflexes. He had a normal brain MRI, and his chest CT showed bilateral pleural effusion, consolidation, and ground glass opacities. Severe motor and sensory neuropathies were discovered after electromyography and were treated with IVIGs[32].

Another 54-year-old male presented with weakness in both lower limbs, after treatment of his fever and dry cough with steroids and amoxicillin. He had a positive rhinovirus PCR test, and his MRI showed bilateral lung opacities. He was diagnosed with GBS, eventually required ventilatory support, and treated with IVIGs[33].

Miller-Fisher Syndrome (MFS)

Miller-Fisher Syndrome is an acute onset of external ophthalmoplegia, loss of tendon reflexes, and ataxia[34]. Most of the MFS cases are preceded by upper respiratory infections like those that occur before the GBS[34].

The development of MFS with COVID-19 can be explained by the COVID-19-associated immune injury/pathway (CSS) or the direct COVID-19 neuropathogenic effect[34].

COVID-19 may trigger the host's immune response with subsequent production of antibodies against COVID-19, which cross-react with the gangliosides (sialic acid-containing glycosphingolipids located on the neuronal cells surface), leading to either autoimmune destruction of myelin sheaths or axons[54,55]. Fantini et al[56] reported cross-reaction between the COVID-19's spikes saccharides and myelin sheaths or axons gangliosides.

A 50-year-old male developed an acute onset of double vision, peri-oral numbness, and ataxia 5 days after an attack of fever and cough. He had right ophthalmoparesis and right oculomotor palsy on examination. The patient's PCR test for COVID-19 was positive. The CSF examination and the brain CT were both unremarkable. He was diagnosed with MFS and treated with IVIGs[34].

Another case presented with diplopia, bilateral 20/25 visual acuity and bilateral abducens palsy. The CSF examination was normal, but the results of the chest X-ray, brain CT, and PCR test for COVID-19 were positive. This patient's polyneuritis was treated with acetaminophen[34].

The above-mentioned cases support the relation between COVID-19 and both the GBS and MFS.

Acute Cerebrovascular Disease (CVD)

Acute Cerebrovascular Disease is one of the neurological manifestations of severe COVID-19 infection. Acute CVD presents as a stroke in 5.7% of patients with severe COVID-19, according to Mao et al[2] (ischemic strokes are more common than hemorrhagic strokes).

COVID-19 produces a state of sepsis-induced coagulopathy, with subsequent organ damage and stroke[57].

To avoid thrombotic events, thromboprophylaxis was recommended for the COVID-19 patients admitted to intensive care units[58]. Strokes and neuronal damage can also occur following the COVID-19-associated CSS[59].

Oxley et al[37] described five cases of stoke. Four were under 50 years old and had no prior history of CVD and/or accidents. They were diagnosed with COVID-19-related stroke since they had positive COVID-19 PCR tests.

Avula et al[38] described a case-series of four patients admitted with strokes (CT-proven strokes), and positive PCR COVID-19 tests.

Al Saiegh et al[39] reported a young child with COVID-19-related sub-arachnoid hemorrhage, without a history of chronic illness, and a 62-year-old female with an ischemic stroke with hemorrhagic conversion after a positive COVID-19 PCR test without COVID-19 manifestations.

Prompt medical intervention is the main predictor of morbidity and mortality in acute CVD. The stroke and neurology teams should be aware of the neurological impacts of COVID-19 and always employ the appropriate strategies and preventative measures. Considering the COVID-19 outbreak, the care providers should take the appropriate preventive precautions because patients can present with neurological manifestations of COVID-19 without any respiratory symptoms[60].

Conclusions

COVID-19 is a neurotropic virus isolated from the CSF and responsible for several neurological

manifestations. COVID-19 induces a surge of inflammatory cytokines (CSS), and the improvement of COVID-19 patients after IL-6 receptor blocker supports the COVID-19-associated CSS theory.

Considering the rising reports of COVID-19-associated neurological manifestations, it is important to identify and treat neurological symptoms as soon as possible to avoid long-term effects. The care providers should take the appropriate preventive precautions because patients can present with neurological manifestations of COVID-19 without any respiratory symptoms. Future research is warranted to confirm the relationship between the SARS-CoV-2 and the development of neurological manifestations.

Conflict of Interest
The authors declare no conflicts of interest.

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Ethics Approval
Not applicable.

Availability of Data and Materials
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Authors' Contributions
MJ, DA, NT, and YK are responsible for the review concept, PubMed search, literature review, data collection, and final revision before submission for publication. IAA, SS, ZK, and SY are responsible for editing, literature review, and final revision before submission for publication.

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