

COVID-19 and neurological complications: A review

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Abstract

Infections with viruses have detrimental effects on neurological functions, and even cause severe neurological damage. There is mounting evidence that coronaviruses (CoV) as well as SARS-CoV-2 exhibit neurotropic abilities and might cause neurological problems. Neuroinvasive viruses are not fully understood, which makes it important to investigate their impact on the nervous system. In this paper, we review research into neurological complications associated with CoV.

Introduction

On March 11th, 2020, Coronavirus Disease 2019 (COVID-19) was affirmed by the World Health Organization as a pandemic. It was reported at the time as an epidemic disease in Wuhan, Hubei Province, China in December 2019. The cause of the severe acute respiratory syndrome that became known as COVID-19 was a novel coronavirus, SARS-CoV-2.¹ There are seven members in the CoV family and SARS-CoV-2 is one of them which can infect humans,² and it belongs to the equal lineage of CoVs, which reasons SARS; however, this novel virus is genetically distinct. The emergence of COVID-19 is a serious threat to global public health.³

Evidence shows these viruses can affect different human systems such as the respiratory, nervous, hepatic, and gastrointestinal systems.⁴ Neurological manifestations are the second most common symptom after respiratory symptoms⁵ and it can be seen in both severe form and early stage of disease.⁶ Headache, confusion, dizziness, mild cognitive impairment, altered taste, loss of smell, blurred vision, as well as muscle and nerve pain are the most common manifestations in COVID-19 patients.⁷ COVID-19 can develop neurological complications either by direct effect on the nervous system during the acute phase or indirectly by immune-mediated infection, which may

appear even after months following the acute phase.^{8,9} In this review, we summarized the studies that have shown neurological manifestations of COVID-19 in patients.

Pathophysiology

SARS-COV-2 has a large envelope with spiked proteins on its surface. Through these surface proteins, SARS-COV-2 binds to the human angiotensin-converting-enzyme receptor 2 (ACE2) on human cells. Therefore, the presence of ACE2 in humans plays a key role in the entrancing of virus. ACE2 is expressed in many tissues like the lung, kidney, pancreas, small intestine, testicles and vascular epithelial, CNS, including neurons and glial cells.¹⁰ After binding to ACE2, the enzyme TMPRSS2 helps to virion entry and the virion releases its RNA. RNA is translated to proteins which are necessary for the virion and finally the RNA is assembled into a new virion and exits the cell.¹¹

Routes and mechanism of CNS invasion

As mentioned above, evidence suggests that SARS-CoV-2 is a neuroinvasive, neurotropic, and neurovirulent virus to both humans and animals.¹² Because ACE2 exists in different human organs such as central nervous system (CNS) and the endothelial cells, interaction between SARS-CoV-2 and ACE2 receptors leads to invasion into the CNS through different ways, including the olfactory route, the trans-synaptic route, the leukocytic route and the haematogenic route.¹³ SARS-CoV-2 infects olfactory epithelium and reaches the CNS via the olfactory neurons. The high expression of ACE2 and TMPRSS2 on the olfactory epithelium has a significant role in transferring the virus into the CNS through olfactory neurons.^{14,15} The second route occurs when SARS-CoV-2 infects peripheral nerves and the virus uses the axonal transport machinery (retrograde transport) to access the CNS.¹⁶ The third route is about the role of leukocytes. Coronavirus can spread to the CNS via infected immune cells, such as monocytes, neutrophils and T cells.¹⁷ Some evidence shows immune cells can express the binding receptors of coronaviruses. So they serve as the reservoirs for virus particles.^{17,18} About the fourth route is assumed, Coronaviruses can attack ACE2 receptors on the endothelial cells of brain vessels that cause disruption in BBB and viruses spread into the CNS.¹⁹

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The most important injuries in CoV

Hypoxia

Many problems such as hemorrhagic problems or infections can lead to brain hypoxia. Proliferation of virus in lung cells is accompanied by alveolar gas exchange disorders, which cause hypoxia in the brain via enhancing anaerobic metabolism in the brain cells' mitochondria.²⁰ Hypoxia in the brain subsequently causes edema in brain cells, cerebral vasodilation, cerebral blood

flow impediment and headache. If hypoxia continues, brain function will be reduced and drowsiness, bulbar conjunctival edema and more complex problems like coma can be observed.²⁰ Hypoxia may also cause acute cerebrovascular disease such as acute ischemic stroke in a patient. As patients with COVID-19 often suffer from severe hypoxia,²¹ this may lead to subsequent nervous system damage.

Immune injury

High levels of IL-1 β , IL-2, IL-6, IL-7, IL-8, IL-10, IL-17, INF- γ , MCP1, G-CSF, TNF α , and macrophages inflammatory protein 1 α were seen in patient with COVID-19.²² On the other hand, neurotropic viruses can lead to brain damage and chronic inflammation via the activation of glial cells. Glial cells, by producing high levels of inflammatory factors, such as cytokines, chemokines, and other inflammation signals, enhance brain damage. Cytokine storms cause disruption to the integrity of BBB, which provokes the neuro inflammatory process.²³ Additionally, studies showed there is a positive correlation between IL-6 and the severity of COVID-2019 symptoms.²⁴ Activation of immune cells in the brain will cause chronic inflammation and brain damage.

Cognition impairment

Clinical and preclinical studies suggest that bacterial, viral, and toxic inflammation can activate Toll-like receptors in microglia and astrocytes, and finally cause neuro inflammation that may lead to neuronal death and cognitive impairments.²⁵ Neuro inflammation induced by prolonged hypoxia and systemic inflammation lead to damage in brain regions responsible for cognitive functions and behavioral alterations, such as the hippocampus and cortex.²⁶ Delirium as functional brain damage is commonly activated by peripheral infection associated with systemic inflammation and is accompanied by an elevated level of serum pro-interleukins and S100B (as an index for BBB disruption) in elderly patients.²⁷ Neuro inflammation has been implied as an important factor in neurodegenerative disorders²⁸ and psychiatric pathologies, including acute psychosis, schizophrenia, and autism spectrum disorder.²⁹ Some evidence showed that anxiety and depression increased in patients with COVID-19.³⁰ Therefore, COVID-19 can affect the brain and leads to neurocognitive impairments.

Conclusions

According to the fact that receptors,

which are for virus entry, exist on many tissues such as the CNS, the adverse effects of the virus will not be limited to the lungs. As the studies showed, viruses, via altering Blood Brain Barrier (BBB) permeability access to the CNS and leads to different neuronal injuries. Evidence suggests that inflammatory pathways and cytokine storms induce neuronal damage. Effects of cytokine storms are documented in some neurodegenerative diseases and neuropsychiatric complications. In addition, clinical findings in COVID-19 patients showed not only pulmonary problems but also neuronal complications such as epilepsy, intracranial infections, encephalitis, meningitis, dizziness, depression, Parkinsonism, confusion, headache, insomnia, stroke, myelitis, etc. Although these documents are at preliminary stages and we need more information about the virus, special attention must be given to patients with COVID-19 for preventing neurological damage in the future until a specific treatment is available.

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