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How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms

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ABSTRACT

The new coronavirus has spread throughout the world in a very short time and now has become a pandemic. Most infected people have symptoms such as dry cough, dyspnea, tiredness, and fever. However, the Covid-19 infection disrupts various organs, including the liver, kidney, and nervous system. Common neurological symptoms of the Covid-19 infection include delirium, confusion, headache, and loss of sense of smell and taste. In rare cases, it can cause stroke and epilepsy. The virus enters the nervous system either directly through nerve pathways or indirectly through the ACE2 receptor. The neurological symptoms of a Covid-19 infection in the brain are mainly due to either the entry of pro-inflammatory cytokines into the nervous system or the production of these cytokines by microglia and astrocytes. Pro-inflammatory cytokines can cause blood-brain barrier disruption, increase in glutamate and aspartate and reduce GABA levels, impairs the function of ion channels, and finally, high levels of cytokines can cause epilepsy. Understanding the potential mechanisms is necessary to gain better insight into COVID-19 induced seizure pathogenesis and to design the correct treatment strategies to achieve appropriate treatment for seizure and epilepsy.

1. Introduction

Coronavirus or COVID-19 has affected many people around the world and is now a major global health threat. COVID-19 was first reported in December 2019 in Wuhan, Hubei Province, China. In January 2020, the WHO identified it as a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the WHO report on August 2020, more than 19 million laboratory-confirmed cases have been reported in 202 countries. Unfortunately, COVID-19 has resulted in more than 700,000 deaths [1].

The major symptoms in infected people include fever, dry cough, aches, pain, tiredness, chills, headache, anorexia, and loss of smell or taste. Covid-19 can also cause some organs to fail, such as the respiratory system, kidneys, liver, and heart. Cardiovascular complications may include heart failure, irregular electrical activity in the heart, coagulation disorders, and acute myocardial injury [2]. Moreover, in some people, gastrointestinal symptoms (GI) such as anorexia, nausea, vomiting, diarrhea, and abdominal pain are associated with COVID-19 [3]. These symptoms may start before other symptoms such as fever, aches, and cough.

People infected with COVID-19 also may experience neurological symptoms [4] and these neurological manifestations may occur with or without cardiovascular and respiratory symptoms [5,6]. Specific neurological symptoms accompanying the COVID-19 infection include loss of smell and taste, muscle weakness and pain, tingling in the hands and feet, vertigo, delirium, ischemic and hemorrhagic stroke, and seizures.

Epilepsy is one of the most common, sudden, and recurrent neurological disorders, affecting about 50 million people worldwide. The exact mechanisms leading to seizures are not yet completely understood. However, the suggested mechanisms include a severe increase in neuronal excitability following an imbalance in the ion channel function, either as an increase in excitatory neurotransmitters of glutamate and aspartate or a decrease in the γ-aminobutyric acid (GABA) neurotransmitter [7]. Other causes of epilepsy include acute metabolic disorders such as hypo or hyperglycemia, electrolyte imbalance, acute neuronal damage following infection and inflammation, stroke, head trauma, mitochondrial dysfunction, hypoxia, and fever.

Only a few studies have been so far conducted to investigate the underlying mechanism of neurological complications of COVID-19, especially seizures and epilepsy. In the following sections, we discuss the five possible mechanisms of epilepsy induced by COVID-19.
2. COVID-19, Epilepsy and central nervous system inflammation (cytokine storm)

Like all six previous beta-coronaviruses, COVID-19 has the ability to enter the nervous system and causes neurological symptoms. The angiotensin-converting enzyme 2 (ACE2) receptor provides the entry route for the coronavirus to infect human host cells. These receptors are mainly found in the brainstem and are responsible for regulating cardiovascular and respiratory function. Like both the Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), COVID-19 may also enter the brain directly through the olfactory tract without the need for ACE2 receptors [8]. The neural pathway is a very important way for the virus to enter into the central nervous system. Viruses can travel into the central nervous system either by infecting sensory or motor neurons or by anterograde transport machinery, using kinesin and dynein [9]. After the invasion, the virus triggers reactive astrogliosis and activates the microglia to induce a large inflammatory cascade. Virus entry into the central nervous system leads to the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), nitric oxide, prostaglandin E2, and free radicals, and causes chronic inflammation neural hyper-excitability, seizure, and death [10,11]. Inflammatory cytokines exacerbate apoptosis and neuronal necrosis in the central nervous system, specifically in different parts of the hippocampus, and these pro-inflammatory cytokines play a key role in epileptic pathogenesis. They also cause epilepsy by increasing glutamate and decreasing GABA in the cerebral cortex and hippocampus. One of the most harmful effects of these cytokines is the secretion of neurotoxic compounds through the autocrine/paracrine mechanisms. These cytokines increase the entry of calcium into neurons through AMPA and NMDA receptors, thereby increasing the neuronal hyper-excitability and death [12,13].

IL-1β, which expresses in active microglia and astrocytes, produces the highest concentration of glutamate in the synapses, and increasing the release of glutamate from astrocytes or reducing the sequestration of glutamate can lead to neuronal hyper-excitability [14]. Laboratory and clinical observations have shown that pro-inflammatory cytokines have a very important role in the onset and maintaining of epilepsy. IL-1β may also induce seizures by increasing the number of GluN2B subunits in NMDA receptors on post-synapse cells [15,16]. It has been shown that the pathological physiological concentration of IL-1β leads to seizures onset with a resulting decrease in GABA [17]. TNF-α is another pro-inflammatory cytokine released from active microglia and astrocytes. TNF-α increases the release of glutamate from the glia and regulates AMPA receptors [18]. Hyperactive AMPA receptors absorb too much calcium ion and cause neuronal toxicity. Through the endocytosis mechanism, TNF-α not only increases the number of glutamate receptors but also decreases the number of GABA receptors, thereby increasing neuronal excitability [19,20]. IL-6 is the other pro-inflammatory cytokine commonly found in small amounts in a normal central nervous system. However, the stimulation of astrocytes and microglia can lead to an increase in IL-6 production [21]. Other cytokines, such as TNF-α, IL-1β, IFN-γ, and IL-17, amplify and increase the production of IL-6 [42]. When a stroke occurs, a seizure may be caused by a variety of factors, including hypoxia, metabolic disorders, and decreased or increased blood perfusion. Acute ischemia may also generate early seizures by increasing extracellular glutamate concentrations, impaired ion channel function, and BBB damage. The mechanisms involved in late seizures vary and include gliosis, chronic inflammation, angiogenesis, apoptosis and neuronal death, neurogenesis, synaptogenesis, and loss of synaptic plasticity [43,44]. In hemorrhagic stroke, hemosiderin deposits lead to neuronal hyper-excitability and seizures.

Infection of the brainstem with COVID-19 may affect the respiratory and cardiovascular regulatory centers and exacerbate respiratory failure, leading to severe hypoxia. Several data clearly show that acute respiratory distress syndrome and organ failure is the final result of a COVID-19 infection cytokine storm. [24,25]. The combination of hypoxia with pre-existing neuro-inflammation causes severe damage to the hippocampus and cerebral cortex, resulting in neuronal epileptic activity [26-29].

3. COVID-19, Epilepsy and BBB breakdown

Activated glia are not the only source for the production of pro-inflammatory cytokines in SARS-CoV-2 infections in the brain. Cytokines, such as IL-6 and TNF-α, can enter the brain through passive or active transmission. Endothelial cells in blood vessels play an important role in the mechanism of blood-brain barrier (BBB) permeability. COVID-19 infection breaks down the integrity of the BBB, which severely impairs brain homeostasis and leads to neuronal apoptosis and death. On the other hand, the BBB breakdown causes the migration of blood cells and proteins, such as albumin, which disrupt the osmotic balance in central nervous system (CNS) and causes seizure [13,30]. BBB breakdown is the other route of entry of peripheral cytokines to the brain.

The other cause of BBB disruption and seizure-induction by COVID-19 is fever and hyperthermia. Laboratory studies show that high temperatures (> 40°C) have detrimental effects on various cells, especially metabolic active brain cells, including neurons, microglia, endothelial, and epithelial cells. Brain damage due to extreme hyperthermia increases the acute activation of glial cells and BBB permeability [31]. In children with febrile seizure, fever not only raises the temperature of the brain, but also induces the release of inflammatory mediators, especially cytokines such as interleukin-1β (IL-1β) in the brain. High level of inflammatory cytokines have been detected in cerebrospinal fluid and / or plasma of children with febrile seizure (FS). COVID-19 may also affect the likelihood of FS. The virus leads to produce inflammatory cytokines in the brains of children which ultimately leads to FS. It has been shown that the expression of IL-1β in reactive astrocytes at least 24 h after FS is increased [32-34].

4. COVID-19, abnormal coagulation, stroke and epilepsy

Patients infected with COVID-19 have shown some coagulation abnormalities characterized by prolonged prothrombin time (PT), increased levels of D-dimer, and diffuse intravascular coagulation (DIC). Tang et al. reported that 71.4% of the non-survivors and 0.6% of the survivors of COVID-19 showed evidence of DIC [35-37]. Several factors may play a role in coagulation disorders in patients with COVID-19. Persistent inflammatory status in COVID-19 patients acts as an important stimulus for a coagulation cascade. Certain cytokines, including IL-6, activates the coagulation cascade and suppresses the fibrinolytic system. Endothelial damage to the pulmonary and peripheral arteries due to a direct viral attack may be an equally important factor in increasing blood clotting. Endothelial cell damage can activate the coagulation system. Moreover, the immune response can be increased by coagulation disorders. These two processes may act as a vicious cycle to worsen this situation. In addition, the appearance of antiphospholipid antibodies may impair blood coagulation as well [38-41].

Post-ischemic and stroke seizure is one of the causes of epilepsy [42]. When a stroke occurs, a seizure may be caused by a variety of factors, including hypoxia, metabolic disorders, and decreased or increased blood perfusion. Acute ischemia may also generate early seizures by increasing extracellular glutamate concentrations, impaired ion channel function, and BBB damage. The mechanisms involved in late seizures vary and include gliosis, chronic inflammation, angiogenesis, apoptosis and neuronal death, neurogenesis, synaptogenesis, and loss of synaptic plasticity [43,44]. In hemorrhagic stroke, hemosiderin deposits lead to neuronal hyper-excitability and seizures. The BBB can be broken down by damage to the endothelial cells when serum proteins enter the CNS after a stroke. For example, albumin binds to transforming growth factor beta(TGFβ) receptors in the astrocytes, and TGFβ signaling activates [45]. Subsequently, down-regulation of potassium channels Kir4.1 and glutamate transporter occurs. The result of this event is increasing the potassium and glutamate in the synaptic cleft. An increase in extracellular K leads to seizures. When microglial and astrocytes cells are activated, BBB permeability occurs through the production of pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, and TGFβ. This cycle can amplify epilepsy after a...
stroke [46-48]. High levels of glutamate released from ischemic or hypoxic cells into the extracellular spaces may activate AMPA and NMDA receptors leading to neuronal apoptosis or death [49]. GABA is a major neurotransmitter in the nervous system. Decreased inhibition of this neurotransmitter after stroke leads to excessive neuronal excitability. Animal studies have demonstrated post ischemic encephalopathy in forebrain ischemia which can cause damage to the GABAergic system. The striatum is specifically vulnerable to transient forebrain ischemia. The dorsolateral striatum has profound neuronal necrosis associated with a marked decrease in GABA synthesis after global ischemia [50]. Decreased GABA receptors may also lead to hyper-excitability of neural networks and seizure [51]. Studies also show that hypoxia, induced by brain ischemia, may play an important role in the onset of epilepsy, depending on how long it lasts. The AMPA receptor antagonist prevents long-term epilepsy after hypoxia [52,53].

5. COVID-19, mitochondria disturbance and epilepsy

Oxidative stress plays an important role in the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) infection. Oxidative stress is closely related to mitochondria dysfunction, and the role of mitochondria in the pathology of COVID-19 disease has been confirmed [54-57]. There is an interplay between mitochondria, oxidative stress, and inflammation during Covid-19 infection. Inflammatory cytokines increase reactive oxygen species (ROS) production in mitochondria [58]. Some inflammatory cytokines, such as TNF-alpha and IL-6, prominent characteristics of the coronavirus found in COVID-19 serum, promote mitochondrial ROS production in the cell.

Mitochondria are intracellular organs with two inner and outer membranes that play an important role in energy homeostasis. In addition to energy production, mitochondria have a variety of functions, including calcium homeostasis, the production of reactive oxygen species (ROS), the modulation of neurotransmitters in the central nervous system, and the regulation of cell apoptosis [59-61]. There is a reciprocal, cause or consequence relationship between mitochondrial dysfunction and epilepsy. In most types of epilepsy, there is secondary damage to the mitochondria. Mitochondrial dysfunction plays an important role in developing epilepsy. These organelles are responsible for generating energy in the cells, which is important for the normal electrical activity of neuronal and synaptic transmission. Any disturbance in mitochondrial function may lead to abnormal electrical activity of neurons and produce seizures.

6. COVID-19, Electrolytes imbalance and epilepsy

Studies have reported various electrolyte abnormalities in patients with coronavirus infection (COVID-19) [62,63]. Electrolyte imbalance may provide insight into the pathophysiology of COVID-19. The COVID-19 infection is associated with decreased serum concentrations of sodium, potassium, magnesium, and calcium, leading to hypotension, hypokalemia, hypocalcemia, and hypomagnesemia. These disorders, especially hypokalemia, may have severe clinical consequences for the infected patient. Hypokalemia leads to exacerbation of ARDS and acute heart damage [10,64,65].

SARS-CoV-2 binds to its host ACE2 receptor, possibly reducing ACE2 expression, thus increasing angiotensin II, which can increase kidneys excretion of potassium, and eventually leads to hypokalemia. Elevated plasma angiotensin II concentrations in patients with COVID-19 act as mediators of acute lung damage, as previously confirmed in SARS-CoV animal models. Potential factors that exacerbate electrolyte imbalance in COVID-19 patients may include gastrointestinal symptoms such as diarrhea and nausea [66-68].

Seizures are the most common clinical symptoms of electrolyte disturbances and are more common in patients with hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia. In these individuals, successful treatment of seizures begins with an accurate diagnosis of the underlying electrolyte disturbances [69,70]. Early detection and correction of these disorders are essential to control seizures and prevent permanent brain damage. If the electrolyte disorder persists, anti-epileptic drugs (AED) alone is ineffective and inadequate for controlling seizures. The treatment of seizures induced by electrolyte imbalance is determined by the underlying cause and in most cases, AED administration is not necessary until the disturbance is rectified [71-73].

7. Conclusion

The impact of the new coronavirus on various organs is not fully understood. Until a definitive and approved cure or vaccine is found, a better understanding of the Covid-19 mechanism leading to organs failure would help to identify strategies and/or therapeutically treatment options for the infection. The virus can cause complicated disorders in the nervous system, such as seizures and epilepsy. The destructive effects of Covid-19 in the central nervous system are mainly caused by a cytokine storm produced by either the entry of pro-inflammatory cytokines from the periphery into the CNS or the production of these cytokines by activated microglia. Secondary seizures may be initiated after strokes, electrolyte imbalance, increased oxidative stress, and mitochondrial dysfunction in Covid-19 patients. More research is needed to prove the exact mechanism of seizures in Covid-19 patients.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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