

Is There a Linking Cable between COVID-19 and Human Brain Diseases?

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ABSTRACT

The novel Severe Acute Respiratory Syndrome (SARS-CoV-2) was first identified in Wuhan, China- 2019, which spreaded its extensions in whole world and made the world a sulking graveyard. There are seven different types of coronavirus, among which SARS-CoV has evolved itself in the nature and has become a life-threatening infection to mankind. This review is focused for the identification of linkage between the Novel Coronavirus (COVID-19) and human brain diseases. The common symptoms which are reported till now in COVID 19 are: fever, cough, fatigue, anosmia and ageusia. Whereas, the patients with more fatal infection are reported to suffer from acute cerebrovascular diseases, impaired consciousness, skeletal muscle injury, arterial and venous thrombosis and acute necrotizing encephalopathy as severe symptoms. Its exact path for neural manifestation is still not established. However, it was expected to be attached with Angiotensin Converting Enzyme-2 (ACE-2), which interacts with capillary endothelium, thus breaking the Blood-Brain Barrier (BBB) and causing shortness of breath due to scarcity of oxygen. To confirm the exact source and path of neurological connection with COVID-19, there is need of autopsies which will give a light in this darkening situation of the world.

Keywords: COVID-19, Brain, Blood-Brain Barrier (BBB), Acute Necrotizing Encephalopathy (ANE).

INTRODUCTION

Coronavirus Disease 2019 (COVID-19)

Novel Coronavirus (COVID-19), a global pandemic, has made life terrifying in the year 2020. First identified as normal influenza but was further declared as deadly virus in March 2020 that has potential to make the population vanish from the world. Initially, it was reported that it could infect lungs and cause breathing problems, but further, its correlation with brain was also observed in patients having severe symptoms. [1] Therefore, this review article is about the linkage between the COVID-19 and human brain diseases, the path via which it affects the brain and leads to the death of the patient.

A Linking Cable between COVID-19 and Human Brain Diseases

Coronavirus- Graveyard of Era-2020

COVID-19, caused by novel Coronavirus is an increasing global pandemic disease in the world. It initially budded out from China in December 2019 and spreaded its branches all around the world. The Severe Acute Respiratory Syndrome (SARS-Cov-2) virus has been speculated to transmit from bats to humans,

as the evidence of this was found in bats having RaTG13 gene. [1]

In February 2020, Center for Disease Control and Prevention released a short summary that explained coronavirus is named because of its crown-like spikes on its surface. Human coronaviruses were first identified in mid 1960s and there are seven different types of coronaviruses that can infect human population, they are 229E, NL63, OC43, HKU1, MERS-CoV (beta coronavirus that causes Middle East Respiratory Syndrome), SARS-CoV (beta coronavirus that causes Severe Acute Respiratory Syndrome) and SARS-CoV-2 (Novel Coronavirus causing Coronavirus Disease 2019 or COVID-19). People around the world get commonly infected by these types of coronaviruses, but these sometimes infect animals and evolve themselves, that could transmit to human beings and infect them. The recent example is SARS-CoV-2 that has caged the world inside their houses.

It generally started as a common cold influenza virus having common symptoms like fever, cough and fatigue. [2] Other symptoms that came into consideration during this pandemic were anosmia and ageusia, [3] which are still common during common cold and high temperature. Moreover, it was found to be related with the respiratory distress and neurological manifestations in patients with severe symptoms. [4] The patients with more severe infections had acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury. [4]

COVID-19- A Linking Cable with Human Brain

A human brain has three main parts: cerebrum, cerebellum and brainstem. Cerebrum interprets functions like touch, vision, hearing, speech, emotions and control of movements. Cerebellum coordinates the muscle movements, maintain posture and balance. While brainstem, which is relay connecting center between cerebrum and cerebellum to spinal

cord, performs automatic functions such as breathing, heart rate, body temperature, digestion, coughing, vomiting and swallowing. The neurological symptoms observed in COVID-19 positive patients were headache, dizziness, confusion, ataxia and much more. These symptoms were initially considered as the result of inflammatory status and hypoxemia due to COVID-19 pneumonia. [3] Seeing the above scenario, it might be the brainstem that gets affected as soon as the person gets hit by coronavirus, as it is showing symptoms in automatic functions of the brainstem.

In July 2020, Fitsiori et al. reported symptoms like headache, dizziness, confusion, ataxia and much more, initially considered as the result of inflammatory status and hypoxemia resulting from Covid-19 pneumonia. [3] Seeing the above scenario, it might be the brainstem that gets affected as soon as the man gets hit. Symptoms of COVID-19 have left catastrophic impacts on brain and nerves that were seen in patients that have recovered from the disease. [5] The patients who had mild illness later realized that they have trouble in concentration, had confused thoughts and memory issues also, therefore, the virus is potential in causing brain problems such as confusion, loss of consciousness, stroke and seizures. Patients who recovered from severe symptoms showed long lasting impacts such as confusing thoughts, disorientation and dementia. [5] Moreover, abnormal level of blood clotting has lead to brain stroke, as when blood clot is formed in arteries that supply blood to brain, further cuts off oxygen and blood supply to the brain, forming a major complication in the body. Other patients showed brain inflammation, nerve damage, stroke and delirium. [6]

Arterial and venous thrombosis is common phenomenon that is majorly seen in COVID-19 positive patients, especially who are suffering from obesity, diabetes mellitus or had any major surgery in recent past. Even, reports indicated that few pregnant women suffering from COVID-19 they showed fetal vascular thrombosis

because of intravascular fibrin deposition.^[6] Thus, we can interpret that in these COVID-19 positive patients, due to thrombosis, the generated clot can cross the blood brain barrier and that finally leads to scarcity of oxygen supply in brain. As a result, such patients suffer from brain stroke and may succumb to death also.

The symptom which is rarely seen in COVID-19 patients is Acute Necrotizing Encephalopathy (ANE). ANE is a rare type of brain disease that occurs due to secondary viral infections like influenza A, influenza B, novel influenza A (H1N1), varicella, human herpesvirus 6 and 7 (HHV6 and HH7), enterovirus, rotavirus, herpes simplex virus, rubella and measles; among which influenza virus and HHV-6 are the most common.^[7] The first presumptive ANE in association with COVID-19 was first observed in 58 years old female airline worker of USA. She had 3 day history of cough, fever and altered mental status. All of the viral tests came negative except COVID-19. Although, the MRI demonstrated rim-enhancing lesion within bilateral region of thalamus. As initially it was known that ANE predominantly occurs in children but it has been reported in adults too, which is further related to intracranial cytokine storms that lead to Blood-Brain Barrier (BBB) breakdown but without direct viral invasion.^[8] ANE can also occur in cerebrum, cerebellum and brainstem other than thalamus.^[8] Further, the radiology medical staff also suggested that we should keep a check on the mental status of the COVID-19 patients after they recover from the disease.^[8] The above given example has illustrated that there is an altered mental status in the Covid-19 patients and it has been reported all around the world, whose severe consequences were brain stroke in the patients having severe symptoms. Therefore, one can state that neurological complications of COVID-19 may include delirium, brain inflammation, stroke, and nerve damage, according to a study which says some of these symptoms may not be a

direct consequence of the novel coronavirus infection but due to the immune system acting on healthy cells.

Mechanism for Neuro-infection via SARS-CoV

The patients who were severely infected by the COVID-19 disease were more prone to the neural infection. The evidence of this viral infection in the brain was first seen in March 2020, in Beijing, China. The presence of this virus has been reported in cerebrospinal fluid, which suggested that SARS-CoV-2 has potential to invade the brain.^[9] The mechanism through which it invaded the brain was its ability to enter host cells by interacting with Angiotensin Converting Enzyme-2 (ACE-2). ACE is a central component of renin-angiotensin system that controls blood pressure by regulating fluid volume in body. It has major role in converting angiotensin-I to active vasoconstrictor angiotensin- II. Therefore, ACE indirectly increases blood pressure by constricting the blood vessels. In order to prevent this, ACE inhibitors are widely used for cardiovascular treatment. Ding et al. 2004, Gu et al. 2005 and Xu et al. 2005, detected SARS-CoV infection in neurons, which suggested the distribution of ACE-2 in the Central Nervous System (CNS). Further, the presence of ACE-2 in brain was reported by Gallagher et al., 2006 in glial cells through cell culturing, which confirmed the presence of ACE-2 in brain.^[10] One can conclude that potential of this virus to infect neurons in brain was detected much earlier than this pandemic.

SARS-CoV has potential to infect the brain due to the abundant expression of ACE-2 throughout the brain. It might get interacted with ACE-2 in the capillary endothelium, which could cause BBB destruction, hence, making its way into the CNS, called as hematogenous route.^[9,11] The other way of entry to the CNS was thought to be via olfactory nerves through nasal cavity that might infect neurons that control breathing process, shown in Figure 1.^[9] Moreover, previous reports also

imparted the light on ACE-2, which is not solely susceptible to infection as virus has potential to infect cells that do not express ACE-2 like hepatocytes in liver. [12] The evidences from the earlier studies revealed that SARS first invades peripheral nerves and then encaves its way to CNS via synapse- connected route. However, the experimental studies by Netland et al.

(2008)on mice, revealed that, when mice were treated with low dose of SARS-CoV, virus particles were first detected in brain instead of lungs, a major aspect for the high mortality rate. [13] In this regard, it is still a mystery for this particular route through which SARS-Cov invades its way to the human brain!

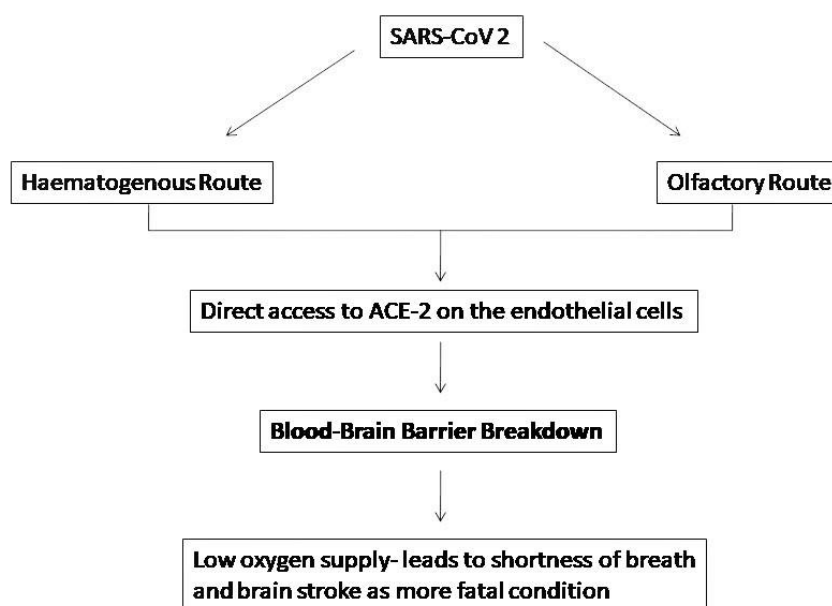


Fig. 1. The diagrammatic presentation of SARS-Cov-2 affecting the brain, by damaging Blood-Brain Barrier (BBB)

CONCLUSION

Hence, taking all the above findings together, we can conclude that neurological consequences are seen in mild as well as severe symptomatic COVID-19 patients, with shortness of breath and brain stroke as more fatal condition. Therefore, there should be no reliability in testing the patients who are suffering from obesity or diabetes mellitus or having onset of the mild symptoms, in order to prevent the spreading of this fatal virus, Covid-19. Further, we found that it is the distribution of ACE-2 in the brain cells that disrupts BBB and leads to neural manifestation. Moreover, there should be an inclusion of neurological expert to keep a check on the mental status of the COVID-19 positive patients and also

its after consequences. As still the exact track of brain infection is not known, so there should be more autopsies performed in order to get source and path of COVID-19 neural infection which is forming the world a sulking graveyard.

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