

## Brain Microenvironmental Changes Associated with the COVID-19 May Act as a New Medical Hypothesis to Explain the pathogenicity of the COVID-19

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### Abstract

COVID-19 has become the most important medical news at global level. Although it is well-known that its impacts are more likely to occur in the respiratory system, the appearance of neurological symptoms in patients with COVID-19 raised important questions as if the virus infected human brain or if it is a matter of overstimulation of the infection. Although studies showed controversial findings, autopsy findings of people with COVID-19 have confirmed the existence of the virus in the brain tissue. We have postulated our hypothesis in which the pathogenicity of the virus implied that some microenvironmental and cross-talks exist to facilitate the pathology of COVID-19. Interactions with receptors in the astrocytes such as ACE2, NRP1, and BSG to facilitate the invasion of the virus have been reported. Other biochemical changes in metabolic pathways such as Glycolysis/Gluconeogenesis, and carbon oxidation have been reported in relation with pathogenicity of the COVID-19. Taken together, COVID-19 infects brain cells and induce microenvironmental changes by potential cross-talks with various components to facilitate its existence and pathogenicity.

**Keywords:** COVID-19; Medical Hypothesis; Pathogenicity; Glycolysis; Gluconeogenesis

### Introduction

Coronavirus disease-19 (COVID-19) is a disease caused by infection with the coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). Despite the fact that COVID-19's most common symptoms are respiratory and linked to pulmonary infection, a growing body of evidence has shown that the SARS-CoV-2 could have effects outside of the lungs [1], like the central nervous system (CNS). Notably, over 30% of COVID-19 patients admitted to hospitals develop neurological and even neuropsychiatric symptoms [2,3], ultimately presenting with encephalitis [4]. According to one study, more than half of these hospitalized patients also have neurological problems three months after completing the acute stage [5]. After being discharged from the hospital, patients' memory was also found to be affected [6]. The neurological disorder is associated with severe nervous system damage [7].

Patients with COVID-19 can experience neuropsychiatric and neurological symptoms. Anxiety and cognitive dysfunction are present in 28 - 56% of COVID-19 convalescents with moderate respiratory symptoms, and that these symptoms are related to changes in cerebral cortical thickness. Histopathological symptoms of brain injury were found in 25% of people who died of COVID-19 using an independent cohort. SARS-CoV-2 infection and replication were found in all of the affected brain tissues, especially in astrocytes. Human astrocytes

derived from neural stem cells are susceptible to SARS-CoV-2 infection *in vitro* through a spike-NRP1 (Neuropilin-1) interaction. Infected astrocytes with SARS-CoV-2 showed improvements in energy metabolism, main proteins and metabolites used to power neurons and neurotransmitter biogenesis, as well as a secretory phenotype that reduced neuronal viability. The hypothesis that SARS-CoV-2 enters the brain, infects astrocytes, and causes neuronal death or dysfunction is further supported. These mechanisms are likely to play a role in the structural and functional changes in COVID-19 patients' brains [8].

Previous research on patients with Severe Acute Respiratory Syndrome (SARS) found the SARS coronavirus in the brain tissue and cerebrospinal fluid of those who had neurological symptoms [9]. Furthermore, changes in the prefrontal cortical loss of white matter, axonal damage, and an area compatible with viral infection have all been observed [10]. Recent evidence showed the existence of viral proteins in human brain regions of COVID-19 patients and in the brain of K18-ACE2 (Angiotensin-converting enzyme 2) transgenic mice infected with SARS-CoV-2 [11,12], indicating that SARS-CoV-2 could have neurotropic properties. SARS-CoV-2 infection has been linked to major astrogliosis, microgliosis, and immune cell aggregation in the human brain [11]. Song and colleagues demonstrated that SARS-CoV-2 infects human brain organoid cells in culture, suggesting that the virus can infect CNS cells [12].

The results showed that at the CNS, astrocytes are the primary sites of viral infection and replication. Infected astrocytes with SARS-CoV-2 showed substantial metabolic changes, including a decrease in metabolites used to power neurons or create neurotransmitters. Infected astrocytes also release an unknown agent that causes neuron death [8].

A thinner cortex in these areas is linked to poor verbal memory capacity. Overall, our results show substantial improvements in cortical structure in COVID-19 patients with moderate to no respiratory symptoms, which are related to neuropsychiatric symptoms [8].

### The existence of neuropilin-1 (NRP1) is necessary for SARS-CoV-2 infection of astrocytes

The entry mechanism by identifying the cellular receptor because astrocytes are susceptible to SARS-CoV-2 infection was investigated. The expression of classic SARS-CoV-2 receptors like ACE-2 as well as alternative receptors like NRP1 and Basigin (BSG) using a publicly accessible dataset of single-cell RNAseq from brain samples of COVID-19 patients was investigated [13,14]. These studies showed that ACE2 mRNA was undetectable in astrocytes, which corroborated previous studies [11,13]. However, astrocytes do express NRP1 and BSG mRNA at detectable levels. It was also discovered that astrocytes from COVID-19 patients have higher levels of NRP1 and BSG mRNA expression than controls. These findings back up the hypothesis that by interacting with the NRP1 receptor, SARS-CoV-2 infects human astrocytes. Pathways that are active include glycolysis/gluconeogenesis as one of the most enriched in carbon metabolism, as well as the Pentose Phosphate Pathway, which indicates a change in glucose metabolism that are involved in the pathogenicity of COVID-19. Carbon oxidation, and oxidative stress are both pathways linked to neurodegenerative diseases associated with COVID-19 [8].

SARS-CoV-2-infected astrocytes' conditioned medium decreases neuronal viability. Astrocytes are important in maintaining brain homeostasis not only because they are the brain's main energy reservoirs, but also because they play a key role in the brain's defensive mechanisms. answer to sterile inflammation or infection-induced cell damage [15,16].

Doctors worked to keep patients breathing in the early months of the COVID-19 pandemic, focusing instead on treating the disease. The lungs and circulatory system are also harmed, and so, there is evidence for neurological disorders. The results were building up. Some COVID-19 patients in hospitals were having trouble sleeping delirium: they were perplexed and disoriented and agitated [2].

The first study of someone with COVID-19 who had swelling and inflammation in brain tissues was published in April by a group in Japan [17]. A patient with deterioration of myelin, a fatty coating that protects neurons and is irreversibly damaged in neurodegenerative diseases like multiple sclerosis, was identified in another report [18].

Varatharaj and his colleagues analyzed clinical data for 125 people in the United Kingdom who had COVID-19-related neurological or psychological effects. Sixty-two percent had suffered damage to the brain's blood supply. strokes and haemorrhages and 31% had altered mental states including agitation or persistent unconsciousness, which was often caused by encephalitis (brain tissue swelling). Psychosis originated in ten individuals who had changed mental states [19].

Human coronaviruses are zoonotic (meaning they come from other species) and can cause severe human outbreaks. While they can infect a variety of tissues, respiratory viruses are the most common, causing extreme inflammation and lung pathology (pneumonia and ARDS), which can be fatal. These single-stranded, positive-sense RNA viruses invade epithelial cells through specific docking proteins like ACE2 and transmembrane protease serine 2 (TMPRSS2), and replicate in the cytoplasm, as in the case of SARS. The 26 to 32 kilobase genome acts as an mRNA that is directly translated and encodes a polyprotein, Orf1a, that is cleaved into nonstructural proteins (NSP), which disrupt host immune responses. The cell cycle, replication, and mRNA and protein synthesis are all involved in the cell cycle [20].

Coronaviruses use cellular membranes extensively to escape immune attack and to develop membrane-enclosed virion progeny. After docking at the plasma membrane, viruses enter cells via endosomes, but with the help of nsp6, they manage to exit at the early endosome level, before reaching lysosomes. Autophagy-derived vesicles contain replication proteins (promoted by viral membrane proteins nsp3, nsp4 and nsp6). Virion proteins are transported and assembled in endoplasmic reticulum-Golgi intermediate compartments after being synthesized in the endoplasmic reticulum (ERGIC) [21].

SARS-CoV-2 infected cells were found in a variety of tissues, most notably the lungs, but their presence in the lungs became intermittent as the disease progressed. The upper respiratory tract, heart, kidneys, and gastrointestinal tract were among the SARS-CoV-2-positive organs. An extensive inflammatory response was found in the lungs, heart, liver, kidneys, and brain in histological studies of organs (sampled from nine to 21 patients per organ). The olfactory bulbs and medulla oblongata in the brain showed substantial inflammation. Thrombi and neutrophilic plugs were found in the lungs, heart, kidneys, liver, spleen, and brain, and they were most often found late in the disease course [22].

## **Conclusion**

The present study showed that the proposed hypothesis “Brain Microenvironmental Changes Associated with the COVID-19 may act as a New Medical Hypothesis to explain the pathogenicity of the COVID-19” by the interactions of COVID-19 with the brain tissue. Micro-environmental changes in the brain include the interactions with NRP1 and BSG to facilitate the adherence of the virus with brain tissue. However, more studies are required to explore in-depth the pathogenicity of the COVID-19.

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