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Molecular and metabolic changes in neurological manifestations of Post-COVID conditions with special consideration of spectroscopy MR analysis

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Abstract

Post-COVID conditions (PCC) are conditions that continue or develop after acute COVID-19 infection. This review provides a comprehensive overview of current knowledge on the molecular and metabolic basis of neurological manifestations of PCC, with particular emphasis on Magnetic Resonance Spectroscopy (MRS) analysis. MRS is a technique used to measure the concentrations of different metabolites in tissues within the human body (including central nervous system) and may contribute to a more precise understanding of the pathophysiology of this condition and the development of new therapeutic methods.

Running title: Molecular and metabolic changes in Post-COVID

Keywords: Post-COVID, neurology, Pathophysiology, Magnetic Resonance Spectroscopy

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Introduction

In the aftermath of the COVID-19 pandemic, a new dimension of medical and scientific challenges arises, centered around understanding and addressing the complex and diverse set of long-term health effects of post-COVID conditions (PCC). PCCs are defined by Centers for Disease Control and Prevention (CDC) as conditions that continue or develop after acute COVID-19 infection. In this study, we focused on neurological manifestations of PCC.

One of the broadly known terms regarding neurological complications is "brain fog" which is a loose term used to describe a mild memory loss that is inappropriate for a person's age. It may include forgetfulness, confusion, decreased ability to pay attention, inability to focus, and difficulty in processing information. It is estimated that about 22% of the patients suffer from cognitive impairment as a complication of COVID-19 where the term "brain fog" could be applied [1]. In a meta-analysis by Ceban et al., cognitive impairment was observed in individuals 12 or more weeks after COVID-19 diagnosis [1]. Patients with COVID-related cognitive impairment experience a reduced quality of life. Miskowiak et al. found that severe cognitive impairment and executive dysfunction were linked to difficulties in the domains of 'usual activity' and 'anxiety and depression' in the EQ-5D questionnaire [2].

The pathophysiology is deeply connected with SARS-CoV-2 ability to enter the peripheral neural system (PNS) or central nervous system (CNS). The virus can access the CNS through the cranial nerves [3,4], and/or via the hematogenous route. Another factor is that viral infection can cause pathological changes within the CNS, including molecular and metabolic changes. There is overwhelming evidence that SARS-CoV-2 can cause a range of neurological problems and psychiatric symptoms, both during and after the initial stages of infection [5–9].

Magnetic Resonance Spectroscopy (MRS) is a technique used to measure the concentrations of different metabolites in tissues within the human body. It allows the study of metabolic changes that occur in neurological manifestations of PCC in the brain. Insights from MRS can contribute to a more precise understanding of the pathophysiology of this condition and the development of new therapeutic methods. Therefore, this article provides a comprehensive overview of the current knowledge on the molecular and metabolic basis of neurological manifestations of PCC, with particular emphasis on MRS analysis.

Neuroinvasiveness and neurotropism

The neuropathophysiology of SARS-CoV-2 can be explained by three terms: neuroinvasiveness, neurotropism, and neurovirulence. Neuroinvasiveness refers to a virus's ability to enter the PNS or CNS, while neurotropism refers to its ability to infect and replicate in cells of the nervous system. Neurovirulence, on the other hand, refers to a virus's ability to infect the CNS, contributing to the development of clinical diseases of the nervous system, regardless of its ability to invade or infect cells of the CNS.

The virus can enter the CNS through two main routes: cranial nerves or blood vessels. Its ability to infect the CNS has been confirmed by Song et al. [10]. SARS-CoV-2 antigens or RNA have been detected in trigeminal ganglion, olfactory sensory neurons and vagus nerve fibers in humans or animal models [3,4,11,12], which suggest that virus can spread to the CNS via cranial nerves. However, some studies have failed to find evidence of the presence of the virus in olfactory sensory neurons [13]. Moreover, Brann et al. provided evidence that there is no ACE2 receptor expression in olfactory sensory neurons [14]; therefore, this route is highly debatable. SARS-CoV-2 is also able to spread from the blood to the CNS through the blood-brain barrier (BBB). Numerous studies have confirmed the presence of the virus in the blood [15,16]. It has also been shown that the BBB is dysregulated in COVID-19 and allows the virus to penetrate the CNS and cerebrospinal fluid [17,18].

SARS-CoV-2 infects cells of the CNS. In humans, viral antigens and RNA have been detected in brain tissues at various locations [10,19]. Additionally, a study performed by Song et al. [10] provided evidence that the virus uses ACE2 receptors to invade CNS cells. Although the ACE2 receptor is expressed in different parts of the brain and in different types of cells [20,21], studies have suggested that the virus does not infect all of them at the same level [10,19,22]. It may be that some cells are more susceptible to infection than others.

Neurovirulence

Various factors have been suggested as the cause of neurological changes in PCC, including neuronal and glial dysregulation, microvascular disease with BBB disruption, hypoxia and related metabolic changes, autoimmune reactions, reactivation of latent herpes viruses, and gut dysbiosis.

SARS-CoV-2 infection can cause a systemic and neurological inflammatory response, which can persist for months after the acute phase [23]. Elevated levels of cytokines, such as IFN-γ, IL-6, TNF-α, IL-10, and chemokines, were observed in the cerebrospinal fluid after infection, as well as increased activity of microglial cells [24]. These factors can contribute to impaired hippocampal neurogenesis and loss of oligodendrocytes and myelinated axons [24–26]. Reactive microglial cells can influence neurogenesis directly through cytokine secretion and indirectly by decreasing the expression of neurotrophic factors and inducing the cytotoxic activity of astrocytes, which can kill oligodendrocytes [24,27]. Additionally, studies performed on human brain organoids have suggested that infected cells can in-

duce local hypoxia, causing the death of neighboring covid-negative cells [10]. Autopsy studies have confirmed this mechanism [10].

Small-vessel thrombosis appears to play an important role in the pathogenesis. Pretorius E. et al. showed that COVID patients have large amyloid clots resistant to fibrinolysis in plasma samples [28]. It could effectively block tiny blood vessels, decreasing blood flow to the brain and leading to ischemic damage. In addition, after the acute phase of the infection, patients show increased endothelial progenitor cell production and increased levels of the von Willebrand factor antigen, propeptide, and thrombomodulin, which are markers for endotheliopathy [29,30]. Endotheliopathy can be caused by persistently elevated cytokine levels and oxidative stress [31], complement activation by immunoglobulin complexes [32], and invasion of endothelial cells by SARS-CoV-2. In infected cells, the main protease of the virus (Mpro) can induce endothelial cell death by acting on the NEMO protein [33]. Along with neurovascular injury, dysregulation of the BBB and disruption of the basement membrane have been observed in COVID [17,18].

T-cell expansion and exhaustion are yet another possible mechanism that affects the brain tissue. T-cells can assume a certain cytokine profile, along with increased inhibitory transcription factor expression and decreased effector function. All factors result in lower responsiveness in chronic infections and even BBB disruption, causing the propagation of inflammation [34–36]. Another hypothesized mechanism involves the generation of antibodies. It is most likely a product of distinct inflammatory reactions [37]. Immunoglobulin G and A antibodies against cytokines, angiotensin converting enzyme 2 (anti-ACE2) and nuclear proteins (ANA) have been detected in COVID patients. ANA have been connected with COVID brain fog [38], and anti-ACE2 have been associated with malignant hypertension causing ischemia [37].

Zuo et al. showed that SARS-CoV-2 infection can lead to gut dysbiosis [39], which, together with enterocyte invasion, can alter the production of microbiota-derived L-DOPA [40]. It is possible that this can cause neuropsychiatric symptoms.

Some studies have suggested a role of reactivation of latent herpes viruses (especially Epstein-Barr virus and Varicella Zoster virus) in the development of neurological symptoms in PCC [34,41–43].

Magnetic Resonance Spectroscopy

MR spectroscopy is a noninvasive procedure used to map metabolic changes in patients with neurological disorders. It can provide beneficial data concerning the underlying pathogenesis of white and gray matter pathologies. According to Sun et al., MR spectroscopy in some conditions can detect neurochemical abnormalities, even when structural MR is inconclusive [44]. The technique of MR spectroscopy consists of imaging protocols including sagittal and axial T1, proton spin density, and T2-weighted spin-echo with or without gadolinium contrast injection, and coronal and/or axial fluid-attenuated inversion recovery (FLAIR) images with or without axial diffusion-weighted imaging (DWI) [45–47].

MR spectroscopy gauges the frequency of metabolites in parts per million and visualizes them as peaks on a graph. This method is useful for distinguishing between various types of shifts in brain structures by comparing the ppm of each metabolite to the ppm of normal brain tissue. The main metabolites used to asses COVID patients are choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), myo-inositol (mI), glutamine (Glu)/glutamate (Gln), and GABA and lactates (Lac) [45,46,48,49]. Another metabolite, glutathione (GSH), was introduced into MR spectroscopy by Samkaria, Avantika et al. as an immediate factor enhancing SARS-CoV-2-induced oxidative damage [50].

Specific metabolic changes have been described in COVID patients by Rapalino et al. They also showed NAA reduction, Cho elevation, and Gln/Glu elevation [48]. Whereas Ernst et al. found reduction in Gln/Glu [49] and thus implying that Gln/Glu shifts are inconclusive in COVID patients. NAA is mainly synthesized in neural mitochondria and can be used as a marker of neuronal integrity in the brain [51]. Therefore, these shifts may have been caused by mitochondrial dysfunction [49]. Elevated Lac was found to be increased in a study conducted by Reda et al. [46], which could be the aftermath of oxidative stress in brain cells after a period of hypoxia.

Conclusions

In conclusion, the neurological manifestations of PCC are a complex and evolving area of research, demanding continued investigation to unravel the intricacies of its pathophysiology. The possible pathophysiologies listed in this article include glial dysregulation, microvascular disease with BBB disruption, hypoxia and related metabolic changes, autoimmune reactions, reactivation of latent herpes viruses, and gut dysbiosis. The changes associated with hypoxia are found in MRI Spectroscopy. This understanding is crucial for the development of effective therapies and interventions to mitigate the long-term effects of COVID-19 on neurological health.

Ethical approval
This conducted study is not related to either human or animal use.

Acknowledgments
Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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