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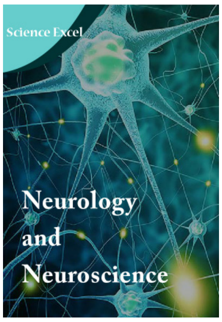

Possible Effects of Inflammation by Covid-19 on the Human Brain

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Abstract

The immune system's inflammatory response is a crucial defense mechanism against infectious agents. At the onset of the pandemic, researchers primarily focused on the respiratory consequences of coronavirus, while overlooking the virus's impact on other organs, such as the brain. However, it is now apparent that post-covid sequelae can persist, especially in those who suffered severe forms of the disease. These symptoms include memory impairment, excessive fatigue, and mood swings. This study examines the possible link between the brain's inflammatory response and these prevalent sequelae, as well as strategies to improve the quality of life for those affected.

Introduction

Inflammatory responses are crucial for protecting the body against various stressors and maintaining physiological integrity [1-3]. Through innate and acquired immunity, these defense mechanisms have evolved to enable humans to adapt to a wide range of inflammatory and infectious agents, preventing potential lethality that would result from a lack of adequate immunological resistance.

During the COVID-19 pandemic, although the number of deaths caused by the SARS-COV-2 virus was impactful on the global population, it was still much lower than it would have been if not for the human adaptable defense system's quick response.

However, inflammatory responses resulting from coronavirus infection in some organs, such as the brain, require careful consideration when discussing the long-term effects of the virus. The scientific community has termed this "long COVID" or post-COVID syndrome, about which research can provide more information about the neurological effects of the virus and its physical and mental consequences [4]. Due to the nature of the virus infection, an overproduction of pro-inflammatory cytokines occurs, resulting in an excessive migration of defense cells to the inflammatory site to fight infection. This process is immunologically important and expected, but there is an exacerbated inflammatory response, leading to an increase in the migration of neutrophils to the site of inflammation and an excess production and release of proteolytic enzymes at the site. This can cause various problems in a variety of inflammatory diseases [5,6].

This attention is relevant because once proteolytic enzymes are released, they act on the inflamed tissue, promoting significant tissue injury. Specifically in the brain, this becomes an aggravating factor for post-COVID sequelae. The brain has a large blood perfusion, making this exacerbated response promote even more tissue injury, leading to physical, cognitive and emotional decline.

Virus-induced brain inflammation

There are increasing reports of COVID-19-positive individuals, whether hospitalized or not, experiencing prolonged loss of smell, short-term memory changes, and persistent cognitive symptoms [7]. One plausible explanation for this is that the virus infects individuals through the respiratory tract and enters through the nasal cavity, which has a protective pseudostratified epithelial lining that is not completely effective against viral infection. The upper third of the nasal cavity contains the olfactory region, which has an olfactory epithelium rich in nerve endings and filaments from olfactory nerves that have receptors for the virus. When the SARS-CoV-2 virus infects the body, the brain becomes a target for the virus due to its proximity to the nasal cavity through the olfactory nerves. The virus can easily disseminate through the brain and replicate in cells, which leads to an increase in viral load and the potential for infection. This viral process is associated with cognitive and emotional deficits that cause the main symptoms of post-COVID syndrome [8,9].

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The effects of COVID-19 on the human brain

The impact of COVID-19 on the brain is not fully understood, but it is clear that the pandemic has caused significant physical and mental health concerns for the population. The most common symptoms associated with post-COVID sequelae are the loss of smell and memory alterations. Both symptoms are related to specific areas of the brain that are important for neurogenesis: the olfactory bulbs and subgranular regions of the hippocampus. These areas have an abundance of neural stem and progenitor cells that can differentiate into neurons, as well as proteins like BNDF and FNT, which modulate the process of neurogenesis [10,11].

The intensity of neurogenesis in these areas is a significant evolutionary gain for the human species because they relate to adaptive behaviors such as feeding, reproductive, and emotional responses. COVID-19 compromises the epithelium and olfactory bulbs, leading to anosmia, the most common post-COVID sequelae.

The hippocampus is an important neurogenic site and relates to deficits in memory, which are commonly reported even with mild forms of the disease. The hippocampus is part of the limbic circuit and has afferent relationships with other areas such as the amygdala and hypothalamus (Figure 01).

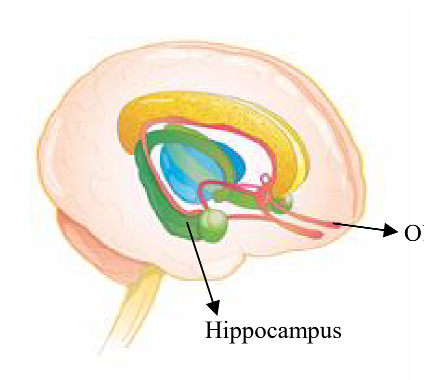

Figure 01: *Important neurogenic sites affected by SARS-COV-2. Source: The author of article.*

In human primates, the most anterior projection of the hippocampus shows an increase in area with a greater population of neurons that enable greater information storage capacities, which are essential for the development of the species [12].

Recent studies in behavioral neuroscience highlight the evolutionary aspects of human memory as an extremely relevant factor for mental health and quality of life [13,14]. Thus, even transient and short-term alterations are impactful for the cognitive and emotional decline, affecting personal and professional relationships. Considering COVID-19 infection, the exacerbated inflammatory response, and the alarming impacts on mental health, it is recommended to evaluate the psychopathological consequences on individuals diagnosed with post-COVID syndrome and to further basic research on inflammation biomarkers and behavioral changes to diagnose and treat emerging psychiatric conditions.

Environmental enrichment as a post-covid syndrome treatment strategy

Environmental enrichment refers to any stimuli that challenge the brain to stimulate neurogenesis and neuroplasticity [15]. Neurogenesis is a natural process in growing and developing brains [16], while neuroplasticity is an adaptive phenomenon where the brain can alter its structure and function [17] through the formation of new dendritic spines and collateral axonal branches. This ability enables memory retention and consolidation, determining the learning process. Studies are being conducted to better understand the impacts of environmental enrichment strategies, including regular physical exercise, new dietary patterns, and everything that has epigenetic potential to modulate neural characteristics.

Moderate to intense physical exercise has shown to be an effective epigenetic factor in modulating the expression of the BDNF protein gene, which is a fundamental molecule in the process of neurogenesis, neuroplasticity, growth, and survival of neurons. It stimulates BDNF synthesis and increases neural plasticity in the hippocampus, improving cognitive processes such as memory and learning. Additionally, physical exercise promotes an increase in melatonin levels, which not only improves sleep quality but also acts as an anti-inflammatory and antioxidant substance, protecting brain tissue [18-21].

Nutrition is also crucial to environmental enrichment. Recent studies show the importance of caring for the intestinal microbiota for the promotion of mental health [22,23], as intestinal dysfunctions, called dysbiosis, directly impact brain development and performance [24].

Dementias that appear earlier and earlier in the population, such as Alzheimer's disease (AD) and Parkinson's disease (PD) may be directly related to intestinal dysbiosis [25-27]. Currently, the Mediterranean diet [28,29], as well as the consumption of foods with high antioxidant and anti-inflammatory properties, represent a significant portion of research investments, as they seek to understand the relationship of natural compounds such as polyunsaturated fatty acids (balance in the intake of omegas 3 and 6, in particular) [30,31], polyphenols [32] and curcumin, which is the main component of Curcuma longa [33;34], for example, with modulation of the inflammatory response and how these molecules can act in the prevention and treatment of neurological diseases.

Final considerations

Studies on the impact of SARS-CoV-2 on the human brain reveal serious sequelae associated with the infection, further research on the relationship between the exacerbated inflammatory response and brain injuries proves necessary. In the US, electronic health records indicate an increase in first-time psychiatric diagnoses within 90 days of a COVID-19 diagnosis, although the cause and effect remain unclear [35]. This highlights the need for enhanced basic and clinical research to better understand the disease's course and its impact on the physical and mental health of the population.

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