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SARS-COV-2 INDUCES PRO-INFLAMMATORY CYTOKINES WITH AN IMPACT ON MENTAL HEALTH

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ABSTRACT

In December 2019, the novel coronavirus strain SARS-CoV-2 caused an outbreak that quickly spread worldwide and led to the COVID-19 pandemic. COVID-19, the severe infectious disease caused by SARS-CoV-2, often presents with symptoms including fever, cough, and mental confusion and can cause the acute respiratory inflammatory disorder. Additionally, viral infection with SARS-CoV-2 is associated with mental health, neuronal degeneration, and psychiatric complications. With infection by the virus, cytokines are released by immune cells, causing acute systemic inflammation affecting the lungs. Lung damage can occur, resulting in hypoxia, brain damage, and mental health dysfunction. In addition, a cascade of inflammatory cytokines, including IL-1, IL-6, and TNF, are released, a phenomenon termed the "cytokine storm" that causes serious pathological damage to tissues and organs and mental health. This exaggerated production of cytokines leads to lymphopenia and disrupts the balance of Treg and Th17 cells, weakening the immune system. The elderly population is particularly at risk for damage associated with the "cytokine storm", which can affect neurological functions or result in death.

KEYWORDS: *SARS-CoV-2, COVID-19, cytokine, mental health, neurodegenerative disease, inflammation, cytokine storm, immunity*

INTRODUCTION

Hundreds of millions worldwide suffer from chronic neurodegenerative diseases with memory impairment in various cognitive domains that can lead to death a few years following the disease. Neurodegenerative diseases are inflammatory disorders, often age-related such as Alzheimer's disease, which leads to memory impairment, but can frequently be unrelated to ageing. However, the pathogenic mechanisms underlying the inflammatory state remain unclear in many cases. Infections, such as viral infections due to SARS-CoV-2, a member of the coronavirus family, are often of great concern because they are associated with mental health, neuronal degeneration, and psychiatric complications (1).

Towards the end of 2019, an outbreak of a novel strain of coronavirus occurred in Wuhan, China, infecting the entire world within a short time. Soon after, this virus was seen to cause Coronavirus Disease 2019 (COVID-19), a severe infectious disease causing an acute respiratory inflammatory disorder that led to the deaths of millions of people

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worldwide, especially in individuals with previous illnesses and those who were in advanced age. Severe infection often presented with symptoms that included fever, cough, respiratory distress, and mental confusion ("brain fog"), frequently requiring hospitalization, including the intensive care unit. COVID-19 is provoked by virus entrance into the body or organs of infected individuals; however, in many cases, people have no symptoms after infection (2) due to an efficient immune response against SARS-CoV-2 (3).

The global spread of SARS-CoV-2 infections in 2020 created great concern and challenges for the healthcare system and the worldwide population, affecting mental health (4). Diverse neurodegenerative (5) and mental health conditions are associated with inflammation and elevated levels of pro-inflammatory cytokines, including depression (6), obsessive-compulsive disorder (7), generalized anxiety disorder (8), and post-traumatic stress disorder (9).

Inflammation in SARS-CoV-2

With SARS-CoV-2 infection, immune cells release cytokines and cause acute systemic inflammation, including the lungs. This process may also involve autophagic modulation, a "self-eating" effect due to digestion that occurs inside lysosomes, inducing lung inflammation (10). After digestion, the degradation products are translocated into the cytoplasm, allowing cellular homeostasis maintenance. Autophagy dysregulation can occur in many pathological processes, including infections and neurodegeneration (11). The virus often induces endothelial dysfunction, complement cascade hyperactivation, diffuse microvascular thrombi in multiple organs, and activation of pro-inflammatory cytokines causing the "cytokine storm" (12).

In the inflammatory process, the pathogenic virus activates the complement through the antibody-mediated pathway, which stimulates the complement component 1 (C1) complex, activating C4 and C1r (13). During a series of cascade reactions, C4b leads to the formation of C3a, which mediates chemotaxis and activates inflammatory cells with induction of cytokine production and degranulation of mast cells (MCs), resulting in enhanced vascular permeability and local blood flow (13). Elderly people with neurological disorders may present with an inflammatory state with a systemic emphasis on the disease, damage to the central nervous system (CNS), and psychiatric dysfunction (14).

SARS-CoV-2 can infect innate immune cells, making them less efficient, and can also affect endothelial cells of the blood-brain barrier (BBB) and other tissues and organs. By infecting the peripheral nerves, SARS-CoV-2 gains entry into the CNS and spreads into the olfactory bulb, cerebral cortex, and spinal cord, with subsequent encephalitis (15). One of the fundamental effects caused by the virus is lung damage resulting in hypoxia, which can lead to brain damage and mental health dysfunction (16). In addition, the inflammatory damage caused by cytokines, such as interleukin-1 (IL-1) (17), tumor necrosis factor (TNF) (18) and IL-6 (19), can also affect the nervous system (20).

The "cytokine storm" affects mental health

The "cytokine storm" is induced by a cascade of inflammatory cytokines that cause serious pathological damage to organs and tissues, compromising the health of the infected population, particularly the mental health of the elderly (14). The main pro-inflammatory cytokines released in COVID-19 are IL-1, IL-6, and TNF, and these trigger the activation of other cytokines, aggravating inflammation and affecting general health.

In the elderly, the "cytokine storm" causes severe pathological effects on organs and tissues and damages neurological functions (14). These effects can be lethal, but even the low-grade inflammatory state can harm this population and aggravate the mental state that is often already in suboptimal health conditions.

The pro-inflammatory cytokines induced by the virus, particularly IL-1, IL-18, TNF, and IL-6, can activate the microglia in an autocrine way and produce IL-2, interferon-gamma (IFN-γ), and other cytokines and chemokines (21) which damage the BBB. These pathological phenomena cause tissue neurodegeneration and induce symptoms of depression (22), effects that, in some instances, can become chronic. Under these circumstances, macrophages, perivascular mast cells (MCs) and endothelial cells are activated, and releasing cytokines affect the vagus nerve and hypothalamus (23).

Pro-inflammatory cytokines IL-1, IL-6, and TNF are often seen in elevated levels in individuals with depressive disorder (24). Cytokines can activate the mechanisms of depression by reducing the mammalian target of rapamycin (mTOR) (25). The mTOR signaling pathway regulates diverse cellular processes such as growth, homeostasis, and disease pathogenesis (26). Decreased mTOR facilitates infectious activity, even if, on the contrary, it seems that the mTOR activity can lead to the activation of some pro-inflammatory cytokines such as IL-6 and TNF (27). mTOR is also involved in reducing viral proliferation and, therefore, in decreasing the pathological phenomenon induced by SARS-CoV-2 (28). Virus-induced hypoxia in COVID-19 leads to the induction of a biochemical cascade that begins with the "regulated in development and DNA damage response-1" (REDD1), which is a stress-response gene and leads to the formation of mTOR (29,30).

Cellular activation in COVID-19

One of the characteristics, particularly of the elderly COVID-19 patient, is the pathological presence in the peripheral blood of lymphopenia and the increase in neutrophilic granulocytes (31), a pathological picture that in severe cases has resulted in the patient's death (32). In these cases, the number of lymphocytes is greatly reduced, such as CD8+ cells, which have α/β, γ/δ T cell receptor (TCR)+, CD3, and other receptors on their surface. These are intraepithelial lymphocytes that can develop intra- and extra-thymically. Most α/β TCRs are enriched through self-reactivity and require β2-microglobulin-dependent major histocompatibility complex (MHC) class I expression for their generation (33). In addition, these cells can have a regulatory function by producing the cytokines IL-10 and TGFβ (34). After activation by antigen-presenting cells (APCs), some CD8+ subpopulations differentiate into cytotoxic T lymphocytes (CTL) cells and memory lymphocytes. Because of this, their deficiency in COVID-19 is very important for the entire immune system, especially for forming antiviral antibodies.

SARS-CoV-2 carries out its pathogenic action using the spike protein S, a glycoprotein that binds to the host cell receptor called angiotensin-converting enzyme 2 (ACE2) receptor (35). Once the virus enters the cell by endocytosis, it releases its RNA, forming a pathogen-associated molecular pattern (PAMP) recognized by pathogen recognition receptors (PRR). The viral antigen is presented to T cells, including Th17 cells, which differentiate and release cytokines by amplifying the immune response (36). Th17 cells have a surface phenotype αβ TCR, CD3, CD4, IL-23R, CCR6, IL-1R and CD161 with functions of promoting protective immunity against microorganisms (37), including SARS-CoV-2, especially at the mucosal surface level. Th17 cells are generated in the presence of TGFβ, IL-6 and IL-21 and are sustained by IL-1 and IL-23. In addition to promoting inflammatory diseases, these important cells can mediate autoimmune diseases (38).

Virus-infected immune cells such as macrophages and lymphocytes produce cytokines such as IFN-γ and chemokines to promote virus clearance and aid the immune response. Excessive production of inflammatory cytokines leads to a decrease in both T and B lymphocytes. Lymphopenia is accompanied by the production of IL-6, decreasing Treg cells and altering the Treg/Th17 ratio. Th17 cells produce the IL-17 cytokine, which activates the generation of other cytokines such as IL-1, IL-6, TNF, and granulocyte G-CSF (39). Hence, Treg cells significantly decrease inCOVID-19, while Th17 cells increase, weakening the immune system (31).

Furthermore, in COVID-19, induced by SARS-CoV-2, various symptoms can occur, such as muscle fatigue with weakness and asthenia (40), cognitive impairment with deterioration (41), mental slowness, attention (42) and execution deficit (43), psychomotor dysfunction and "brain fog" (44,45). In addition, individuals with this disease have impaired social and occupational activity limits.

Conflict of interest

The author declares that they have no conflict of interest.

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