Psychoneuroimmunology in SARS-CoV-2 infection: A Molecular Approach

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Abstract

The human body is constantly at risk from threats like bacteria, viruses, and pollution. While our immune system, especially macrophages, protects us from these threats, overwhelming negative challenges can weaken it, leading to severe diseases. Everyone's immune response varies, making some more resistant to diseases than others. Immunology studies this defence system. Psychoneuroimmunology delves into the connections between psychology, the nervous system, and immunity. Emotional states such as anxiety or stress can weaken one's immune response. The central nervous system (CNS) is particularly vulnerable to viruses. Historically, influenza pandemics have resulted in increased mental health issues, with some debates linking the Spanish flu to neurological consequences. Several viruses, including the herpes virus and coronavirus, can impact the brain. Research has shown connections between chronic illnesses, such as HIV and tuberculosis, and mental disorders like depression. Epidemics like SARS and Ebola have also been linked to widespread behavioural reactions and mental disorders in survivors and healthcare workers. Neuropsychiatric disorders can arise from various mechanisms, like cerebral hypoxia or direct brain infections.

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Introduction

The human body will constantly be threatened by exposure to bacteria, viruses, parasites, solar radiation, and pollution. Usually, we are protected by the body's defence system, the immune system, especially macrophages, and sufficiently complete nutritional needs to support health. Excess negative challenges, however, can suppress the body's defence system and immune system and result in various fatal diseases. Every human being has their own immune system, which means that the human body is not susceptible to disease. Immunology is a study related to the immune system in humans. The immune system can protect a person's body from various infections with a defence.

Psychoneuroimmunology itself is a study that is very closely related to the psychological, innervation system, and immunity of a person. Psychologically, a person turns out to be able to influence how the innervation system works, which, if not well controlled, can actually cause pain. Psychoneuroimmunology is also the basis for learning that an anxious, afraid, and stressed mood can actually reduce a person's immunity.

The central nervous system (CNS) is vulnerable to viruses (Xia et al., 2010). Historically, past influenza pandemics have been associated with a post-infection increase in anxiety, insomnia, fatigue, depression, suicidality, and delirium (Honigsbaum, 2013). Furthermore, there is some debate as to whether the Spanish flu pandemic of 1918 was causally associated with encephalitis lethargica as a neurological consequence (Hoffman & Vilensky, 2017). Other viruses end up reaching the brain, such as herpes virus, arbovirus, coronavirus, measles, and HIV, among others (Xia & Lazartigues, 2010)

Several investigations have indicated a direct relationship between chronic diseases such as human immunodeficiency virus (HIV) and tuberculosis, with mental disorders such as depression (Gale et al., 2018; Mason & Lyons, 2003) in the general population (Kuan et al., 2019; Van Den Heuvel et al., 2013). Similarly, studies conducted during and after epidemics such as SARS 2003 and Ebola 2014 found that there was widespread behaviour induced by the hyperactive reaction among the general public (Person et al., 2004; Shultz et al., 2016). In addition to this, various psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder (PTSD) were found mainly in survivors and healthcare workers (Blakey et al., 2019; Gardner & Moallef, 2015; Mak et al., 2009).

Neuropsychiatric disorders can occur due to different mechanisms, such as cerebral hypoxia, cytokine storm due to exaggerated immune response and encephalitis due to direct brain infection. Nervous system involvement leads to poor prognosis of COVID-19.

Psychoneuroimmunology

Psychoneuroimmunology is a science that can explain the modulation of the immune system under stress in response to behavioural changes (Ader, 2007). This concept is a combination of psycho-neuro and immunology so that there is an interaction between the central nervous system and the immune system mediated by the HPA (Hypothalamus-pituitary-adrenal) axis (Black PH, 1995). Ader also stated that psychoneuroimmunology is a science that studies the interaction

between behaviour, neuroendocrine function, and immune system processes (Putra, 2005). Two-way communication between the nervous system and immune networks can explain that behaviour and stress can affect immunity, and vice versa; immune processes can affect behaviour. Thus, physical, and psychological activity can lead to biological activities of the body, including the body's immune response (Shao et al., 2021).

Robert Ader first introduced the term psychoneuroimmunology during a lecture at the American Psychosomatic Society in 1980. He summarised the research that demonstrated the fundamental unity of the body's immune system to maintain health, and he underlined the fact that the immune system (immunology) is no exception to this general rule. Knowledge of the immune system and how it functions has grown exponentially. This is in relation to how it relates and interacts with various physiological systems, including the central nervous system. An essential focus of neuroimmunology is to elucidate the way in which the immune system influences neural function and, subsequently, behaviour and cognition through the modulation of cytokines and hormones, particularly stress hormones such as corticosteroids. Since the intimate relationship between the immune system and brain function has been revealed, research in this area has been revealed to be extended to psychoneuroimmunology, which specifically addresses the role of the immune system in the development of psychiatric disorders, including depression and anxiety.

The basic concepts of psychoneuroimmunology are that emotional status determines immune system function, and stress can increase the body's susceptibility to infection and carcinoma. It is said further that character, behaviour, coping patterns, and emotional status play a role in modulating the immune system. In the early 1950s, behavioural scientists studied the relationship between behaviour and the immune system, which was extraordinarily complex, and one of the most exciting issues was the relationship between stress and the immune system. Recently, research has developed on the relationship between behaviour, neural work, endocrine function, and immunity. The results of this study further support the concept of psychoneuroimmunology.

Psychoneuroimmunology is an integrated concept regarding the function of immune regulation to maintain homeostasis. To maintain homeostasis, the immune system integrates with the brain's psychophysiological processes and, therefore, influences and is influenced by the brain. Through this approach, the mechanism of interaction between behaviour, the nervous system, the endocrine system, and immune function has begun to be understood. The basic idea of the psychoneuroimmunology concept is that emotional status determines immune system function, and stress can increase the body's susceptibility to infection and carcinoma. It is said further that character, behaviour, coping patterns, and emotional status play a role in modulating the immune system.

Civilisation makes us live in conditions of psychological and physiological stress. Two-way communication between the nervous system and immune networks can explain that behaviour and stress can affect immunity, and vice versa; immune processes can affect behaviour. Thus, physical, and psychological activity can lead to biological activities of the body, including responses. In this case, the term stress is often used to describe psychological (emotional) conditions and biological responses. The term stress is prepared for complex psychological and physiological phenomena that are not yet clearly understood. Stress response occurs when a person faces a stimulus that he perceives as a threat of danger as a stressor.

Stressors are first accommodated by the five senses and transmitted to the emotional centre located in the central nervous system. From here, stress will be channelled to the organs of the body through the autonomic nerves. The pathways through which stress is carried out include hormone glands, and changes in hormone balance occur, which in turn will cause functional changes in various target organs. Several researchers have proven that stress has caused changes in neurohormonal neurotransmitters through various axes such as HPA (Hypothalamic-Pituitary Adrenal Axis), HPT (Hypothalamic-Pituitary-Thyroid Axis) and HPO (Hypothalamic-Pituitary-Ovaria Axis). HPA is the most studied mechanism theory.

Stimulation of the central nervous system will cause the secretion of several neurotransmitters, neuropeptides, and hormones for the operationalisation step of adaptation reactions in cells or subcellular. There is a similarity of capture points at the level of the central nervous system between physical and psychological aspects, so any stressors that affect the body will provide a biological response to the nervous system. So, both physical and psychological aspects can cause the body's biological activities, including the body's immune response.

The immune response is a coordinated reaction by cells and molecules against microbes or other agents. So, when the immune condition decreases, the body's defences will decrease, and the body can be susceptible to disease and then get sick. The suppression of the function of the immune system will cause an increase in a person's susceptibility to infectious diseases.

Disease and immunity mechanisms

The body's immune system is activated by microorganisms or foreign substances (antigens) that are not recognised by the body. Examples of such antigens are bacteria, fungi, and viruses.

1. Recognizing Foreign Substances Entering the Body

When an antigen attaches to an immune cell receptor, the whole body will work together to recognise the antigen and provide a signal to activate each component of the immune system. One of the functions of the immune system is to keep a record of every antigen it encounters for the first time and how to destroy it. These memory cells exist in the form of white blood cells, namely T lymphocytes (T cells) and B lymphocytes (B cells). Because of this memory, when attacked by the same antigen, the body will immediately recognise the disease and immediately expel it.

2. Antibodies Production

Plasma cells from B lymphocytes function to produce antibodies. Antibodies will bind to the incoming antigen, and B lymphocytes will form memory cells that survive in the body. So, when the immune system encounters the same antigen, antibodies will always be ready to fight the antigen.

3. Adaption for Vaccines

The way immunisations or vaccines work is similar to that process. Vaccines will introduce the immune system to disease antigens. So that the body can produce memory cells and antibodies that are ready to ward off antigens anytime and anywhere.

4. Stronger Immune Against Old Antigens

Have you ever wondered why people rarely get chickenpox a second time? This is because these memory cells recognise the chickenpox antigen, so the immune system kills it immediately. Meanwhile, the body does not recognise new diseases such as the COVID-19 virus, and there is no vaccine yet. This virus will quickly attack anyone, especially people with weak immune systems.

5. Killing Antigens

Antibodies from these B lymphocytes do not act alone. Antibodies need the help of T lymphocytes to kill antigens. Think of B lymphocytes as a prison for confining disease antigens. Meanwhile, T lymphocytes as soldiers who kill the antigen of this disease. Even some components of T lymphocytes are also called "T-killer cells" or killer T cells. In addition, T lymphocytes function to convey signals to other cells (such as phagocytes), which also work to "swallow" and destroy viruses.

Immunology and pathophysiology of neuropsychiatric manifestations in COVID-19

Although COVID-19 surprised everyone at the beginning of 2020, and despite the fact that many countries have returned to "normal", the figures leave no doubt that the pandemic has not ended, mainly thanks to the variants that challenge the natural immunity of those who have experienced the disease or of those who have been vaccinated. There are many changes from the original strain both in terms of contagion rate and reinfection, although until now, the reinfection was approximately 90 days, which provided natural immunity; in the last waves in Europe it is estimated that the time of reinfection has been reduced to 30 to 40 days (Sheehan et al., 2021). On the positive side, the mortality rate associated with the infection has fallen drastically, patients hardly have any symptoms in some cases (Abdullah et al., 2022). In this context, in which there is more attention to the variants and about the vaccine doses, it seems that an important social problem is being forgotten that is not being correctly dimensioned, in this case we are talking about post-acute sequelae of covid-19 also known as long covid (Al-Aly et al., 2021). That is, the consequences of covid-19 both among the asymptomatic and symptomatic regardless of the severity of the disease, which although the first studies indicated that it lasted three months, this was extended to six months and later to one year. In other words, a person who has experienced COVID-19 with almost no symptoms can present physiological and neurological problems more than a year after they became infected, which some studies indicate affects 7 out of 10 infected (Bell et al., 2021). This has given a special casuistry, since there are patients who were infected with one variant, compared to others who were infected with another variant; patients who were infected with one variant and reinfected with another; infected vaccinated patients;

infected unvaccinated patients, vaccinated patients without being infected... a whole series of cases that are not being given sufficient follow-up on the effects and consequences of covid-long.

The symptoms found in long COVID are not limited to the respiratory system but to multiple organs of the body and the most frequent are neuropsychiatric, to the point of considering calling Post Covid-19 Neurological Syndrome (PCNS) long-covid. These symptoms in patients after acute COVID-19 are persistent for a long time. In fact, several studies indicate that many patients present symptoms even for a prolonged time after SARS-CoV-2 infection (Carfì A. et al, 2020). About one third of positive patients develop neurological and neuropsychiatric symptoms, generally in the early stages of the disease, but sometimes even after the resolution of the respiratory symptoms (Rudroff T. et al, 2020). The most common symptoms appearing post-infection are anosmia, ageusia or dysgeusia, headache, muscle and joint pain, fatigue and mental fog, symptoms that can last for weeks or months (Rudroff T. et al, 2020). Many causes are at the basis of the neurological manifestations of COVID-19 being a direct effect of the coronavirus on the nervous system and or immune-mediated effects linked to para-infectious or post-infectious mechanisms (Nuzzo D. et al, 2021).

In many patients infected with SARS-CoV-2 and, even more, in those who develop moderate to severe respiratory failure, neuropsychiatric disorders can occur due to different mechanisms that can act concomitantly, such as cerebral hypoxia due to respiratory failure (mental confusion), cytokine storm due to exaggerated immune response (apathy, anorexia and muscular pain) and encephalitis due to direct brain infection (agitation and psychosis) (Ahmed et al., 2020; Gardner & Moallef, 2015; Jain et al., 2020; Katta et al., 2020; Mao et al., 2020; Tejaswi, 2020).
The angiotensin 2-converting enzyme (ACE2) has been identified as the functional receptor for SARS-CoV-2, which is present in multiple human organs, including the nervous system and the musculoskeletal system. The expression and distribution of ACE2 explain why SARS-CoV-2 can produce neuropsychiatric symptoms through direct and indirect mechanisms. Coronavirus encephalitis has also been confirmed, as in SARS-CoV and MERS-CoV. The researchers detected SARS-CoV nucleic acid in the cerebrospinal fluid of these patients and also brain tissue from the autopsies (Arabi et al., 2017; Hamming et al., 2004; Jain et al., 2020; Katta et al., 2020; Tejaswi, 2020; Wu et al., 2009).

Another mechanism involved in many genetically predisposed patients is the cytokine storm generated by the interaction of the immune system with the virus, which, in addition to the systemic repercussion, primarily affects the nervous system. Cytokine storm resembles macrophage activation syndrome (MAS), a severe condition that presents with hypercytokinemia, fever, cytopenia and hyperferritinemia; pulmonary involvement (including ARDS) and is associated with the severity of COVID-19 disease. It is characterized by an increase in interleukin (IL) -2, IL-7, granulocyte colony-stimulating factor, interferon-inducible protein 10-γ, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumor necrosis factor-α (Jain et al., 2020; Katta et al., 2020; Mehta et al., 2020; Tejaswi, 2020).

Brain cytokines produce behavioural changes (sickness behaviour) during the course of an illness or infection, manifesting depressive symptoms such as emotional hyperresponsiveness, apathetic syndrome, anhedonia, hyporexia, weight loss, hypersomnia, alteration of the circadian rhythm, fatigue and chronic pain, psychomotor inhibition, demotivation, disinterest and alteration of higher mental functions, etc. (Dantzer et al., 2008; Debnath et al., 2020; Miller, 2009; Raison et al., 2006). Furthermore, it has been described a high level of this cytokines in blood and in the prefrontal cortex of teenage

suicide victims (Pandey et al., 2012). It would appear that during acute coronavirus infection, immune hyperreactivity generates this behaviour syndrome with such variable neuropsychiatric symptoms. This is important since in terms of COVID-19 infection, beyond the typical symptoms of fever, cough and dyspnea, the neuropsychiatric manifestations are added, which would be responsible for the symptoms of apathy, anorexia, and muscular pain. These symptoms can go as far as the mental confusion, agitation, and psychosis that many patients may manifest even in initial stages, together with characteristic laboratory findings and pulmonary abnormalities (Guan et al., 2020). Most of studies that exist on the COVID-19 pandemic produced by the SARS-CoV-2 coronavirus, report neuropsychiatric symptoms only as part of the manifestation of the disease in its terminal phase. However, there are neuropsychiatric symptoms since the beginning of the disease. Several investigations have indicated a direct relationship between chronic diseases such as human immunodeficiency virus (HIV), tuberculosis, SARS, MERS, Ebola, and SARS 2003 with mental disorders such as depression. Neuropsychiatric disorders can occur due to different mechanisms, such as cerebral hypoxia, cytokine storm due to exaggerated immune response and encephalitis due to direct brain infection. Nervous system involvement leads to poor prognosis of COVID-19.

According to studies reviewed to date, neuropsychiatric symptoms can be divided into symptoms of the central nervous system (CNS), such as headache, dizziness, vertigo, altered consciousness, confusion, ataxia, acute cerebrovascular disease, and seizures; peripheral nervous system (PNS) symptoms, such as anosmia, dysgeusia, neuralgia, and diarrhoea; and psychiatric symptoms such as apathy, depression, anorexia, psychosis, acute confusional syndrome, and agitation.

Several investigations have indicated a direct relationship between chronic diseases such as human immunodeficiency virus (HIV) and tuberculosis, with mental disorders such as depression (Gale et al., 2018; Mason & Lyons, 2003), in the general population (Kuan et al., 2019; Van Den Heuvel et al., 2013). Similarly, studies conducted during and after epidemics such as SARS 2003 and Ebola 2014, found that there was a widespread behaviour induced by the hyperactive reaction among the general public (Person et al., 2004; Shultz et al., 2016). In addition to this, various psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder (PTSD) were found mainly in survivors and healthcare workers (Blakey et al., 2019; Gardner & Moallef, 2015; Mak et al., 2009).

Previous studies have reported adverse psychological reactions to the 2003 SARS outbreak among healthcare workers (Arabi et al., 2017; Hamming et al., 2004; WHO, 2020b; Wu et al., 2009). Studies showed that these health workers feared contagion and infection from their family, friends and colleagues (WHO, 2020b), felt uncertainty and stigmatization (WHO, 2020b; Wu et al., 2009), reported aversion to work (Wu et al., 2009), and high levels of stress, anxiety and symptoms of depression (Hamming et al., 2004), that could have long-term psychological implications (Hamming et al., 2004). Similar concerns are now emerging about mental health, psychological adjustment, and recovery for both the ill and the health workers who treat and care for patients with COVID-19. Besides, as the WHO has highlighted in its state of mental health, stigmatization and the scapegoat of affected people, including health professionals, is very common during epidemics (Rubin & Wessely, 2020; Shigemura et al., 2020). Unfortunately, this trend continues to prevail during the current COVID-19 outbreak, as many people of Asian origin, explicitly Chinese, are victims of xenophobia and social stigmatization, with high levels of threats online and during public interactions (WHO, 2020a).

Conclusion

The field of psychoneuroimmunology offers a comprehensive framework for understanding how psychological stressors, including those experienced by healthcare workers during pandemics, can modulate immune function and contribute to the vulnerability to, and severity of, infectious diseases. The evidence presented underscores the significant impact of psychological states such as stress, anxiety, and depression on immune competence. This relationship is crucial in the context of COVID-19, where healthcare workers face unprecedented challenges, including high levels of exposure to the virus, psychological stress from witnessing widespread suffering, and the fear of transmitting the virus to loved ones. These stressors can compromise immune function, making individuals more susceptible to infections and potentially influencing the clinical course of diseases like COVID-19.

Moreover, the pandemic has highlighted the neuropsychiatric sequelae associated with viral infections, not only due to the direct effects of viruses on the CNS but also due to the immune system's response to infection. Conditions such as "long COVID," characterized by persistent neuropsychiatric symptoms, illustrate the need for a broader understanding of the post-acute consequences of viral infections, which can have profound implications for individual health and public health policy.

Addressing mental health needs as part of the public health response to pandemics is not just worthy, but essential. Pandemics, such as COVID-19, exert unprecedented pressures on populations, including fear of illness, grief from loss of loved ones, financial instability due to economic downturns, and the psychological impact of prolonged isolation and quarantine measures. Interventions aimed at reducing stress and improving psychological resilience among healthcare workers and the general population can have beneficial effects on immune function and overall health. Furthermore, recognizing the potential for neuropsychiatric manifestations of infectious diseases can inform clinical practice and support the development of comprehensive care models that address the full spectrum of patients' needs during and after infection.

In sum, the COVID-19 pandemic has served as a powerful reminder of the interconnectedness of psychological, neurological, and immunological health. As we continue to navigate the challenges posed by this and future pandemics, an integrated approach that considers the psychoneuroimmunological impacts of infectious diseases will be essential for promoting resilience, improving outcomes, and safeguarding the health of individuals and communities.

Competing Interests

The author declares to have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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