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Review article

Investigating the potential mechanisms of depression induced-by COVID-19 infection in patients

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ABSTRACT

The new coronavirus (COVID-19) has emerged now in the world as a pandemic. The SARS-CoV-2 infection causes variant common symptoms, such as dry cough, tiredness, dyspnea, fever, myalgia, chills, headache, chest pain, and conjunctivitis. Different organs may be affected by COVID-19, such as the respiratory system, gastrointestinal tract, kidneys, and CNS. However, the information about the COVID-19 infection in the CNS is insufficient. We do know that the virus can enter the central nervous system (CNS) via different routes, causing symptoms such as dizziness, headache, seizures, loss of consciousness, and depression. Depression is the most common disorder among all neurological symptoms following COVID-19 infection, although the mechanism of COVID-19-induced depression is not yet clear.

The aim of the present study is to investigate the probable mechanisms of COVID-19-induced depression.

The reasons for depression in infected patients may be due to social and pathological factors including social quarantine, economic problems, stress, changes in the HPA axis, inflammation due to the entry of proinflammatory cytokines into the CNS, production of inflammatory cytokines by microglia, mitochondrial disorders, damage to the hippocampus, and malnutrition.

By evaluating different factors involved in COVID-19-induced depression, we have concluded that depression can be minimized by controlling stress, preventing the cytokine storm with appropriate anti-inflammatory drugs, and proper nutrition.

1. Introduction

Coronaviruses are a large family of viruses, including SARS, MERS, and COVID. Seven types of coronavirus that can transmit to humans have been identified. The latest (SARS-CoV-2) started in Wuhan, China in December 2019, and spread worldwide very rapidly. Although most COVID-19 patients initially have mild symptoms similar to the common cold, more severe symptoms appear a few days after infection [1–3]. These symptoms include dry cough, tiredness, dyspnea, fever, chills, headache, chest pain, conjunctivitis, dizziness, sore throat, myalgia, and loss of sense of smell [4,5]. The SARS-CoV-2 infection can be associated with different consequences in the CNS [6]. Nervous manifestations include seizures, stroke, Guillain-Barre syndrome, memory impairment, PTSD, delirium, insomnia, sleep disorder, anxiety, and depression [7,8].

Because more COVID-19 infected patients have flu-like symptoms, more attention has been paid to the respiratory complications, and the adverse consequences in the central nervous system such as seizure and depression have been mostly neglected [9]. The peripheral neural pathways are the most important entrance routes for the virus to the CNS [10,11]. The unique anatomy of the olfactory nerves converts this pathway into a channel between the nasal epithelium and the CNS [12].

It has been reported that some infected patients show non-specific neurological symptoms such as delirium, headache, and loss of consciousness without any signs of respiratory failure [13]. The entry of the virus into the CNS is followed by inflammation. In some conditions, diseases such as MS, seizures, and depression can develop in these patients [11,13,14].

Major Depressive Disorder (MDD) is a common, multifactorial heterogeneous, and chronic complex that affects approximately 350 million people worldwide [14]. MDD causes emotional, behavioral, and physical problems. Common symptoms of depression include boredom, inability to enjoy, feelings of hopelessness, social isolation, and worthlessness. Problems in concentration, inability to make decisions, sleep disorders (insomnia or excessive sleep),

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anorexia, loss of libido, and various physical aches are more symptoms of major depression [15–17]. In patients with COVID-19, most depression symptoms can be clearly seen during the illness and after a partial recovery [18,19].

Anxiety and depression induced by COVID-19 infection can worsen the prognosis of the disease and have a negative effect on the immune system [20].

Previous studies have shown the prevalence of depression in COVID-19 infected patients is 45%, anxiety 47%, and sleeping disturbances 34%. No significant difference was detected between genders [21].

The most important reasons for developing depression in COVID-19 infected patients can be divided into social and pathological factors.

1.1. Psychological mechanisms involved in COVID-19 induced depression

1.1.1. Quarantine

The policy of quarantine leads to loneliness and social isolation, and these two are causes of stress, anxiety, and other psychological complications [22–24]. In experimental animal models, social isolation stress (SIS) alters activity, social behavior, neurochemical function, and the neuroendocrine system. This may cause physiological and anatomical changes in animals. Animals with SIS have been shown to exhibit symptoms of psychiatric disorders such as anxiety, depression, and memory loss. Social isolation stress also activates the hypothalamic–pituitaryadrenal (HPA) axis, which ultimately releases cortisol and catecholamines. In general, SIS is accepted as an experimental method to induce depression in animals [25].

Considering the potential negative impact of quarantine on depression, it is a very important factor in maintaining public health. Receiving support from family, friends, and medical staff can be a major palliative factor that helps patients to deal with stress and depression induced by quarantine [26,27].

1.1.2. Stress

Studies have shown that stress that occurs during a pandemic may play a major role in the development of depression in Covid-19 patients. Stress may be due to psychosocial factors such as the fear of contact possibility with infected people, quarantine, lack of access to tests and medical care, receiving conflicting messages and even constant media coverage of epidemic reports or instructions about public health practices, increased workload, economic problems, and lack of available resources (e.g., masks and personal protective equipment) [27,28].

Elevated blood cortisol concentrations and abnormalities in the Hypothalamus-hypophysis axis (HPA axis) following virus infection are responsible for depression following SARS-CoV-2 infection. Although high cortisol levels may have short-term beneficial effects, enabling the brain to overcome stress, chronically elevated cortisol levels can affect voltage-gated ion channels and increase calcium uptake. Chronic stress is the main factor involved in the development of depression caused by COVID-19. Reducing stress can prevent or reduce depressive symptoms [29–31].

1.2. Central mechanisms involved in COVID-19 induced depression

1.2.1. COVID-19, inflammation and depression

The entry of COVID-19 into the CNS causes uncontrolled activation of microglia, which leads to the release of inflammatory cytokines (TNF-α, IL-6, IL-1B), nitric oxide, prostaglandin E2, and free radicals in the brain. In the case of a severe immune response (cytokine storm), destructive damage in the blood–brain barrier occurs, leading more inflammatory factors to enter the CNS (31, 32) and release even more cytokines from the microglia into the CNS [32–37].

Among pro-inflammatory cytokines, IL-6 (an important member of the cytokine storm) increases during SARS-CoV-2 infection and plays a significant role in the pathogenesis of depression in COVID-19 patients. The concentrations of IL-6 is probably directly related to the severity of depression in infected patients [38,39].

Inflammation induced by COVID-19 can also increase the production of free radicals and decrease the total level of glutathione, which has been previously detected in patients with major depressive disorder (MDD) (42). Pro-inflammatory cytokines also play an essential role in regulating the response to stress and neurogenesis in the CNS as they destroy the neurotrophic support, alter glutamate release, and increase oxidative stress. Finally, these cytokines cause cytotoxicity, neuronal loss, decreased neurogenesis, and neurological complications in depression [41,42].

1.2.2. COVID-19, mitochondria disorder and depression

The mitochondria are damaged by COVID-19 either directly by the hijack of the organelle for transcription of the virus genome or indirectly by increasing pro-inflammatory cytokines and ROS production [40,41]. In the direct way, COVID-19 either induced the localization of its RNA transcripts or RNA itself in the host cell's mitochondria, manipulating mitochondrial function [41].

In patients with COVID-19 inflammatory cytokines, such as TNF-α and IL-6, inhibit mitochondrial oxidative phosphorylation and ATP production and increase ROS production, which may cause impaired mitochondrial function and dynamics eventually leading to apoptosis and cell death .[40]

Mitochondria are very sensitive to oxidative stress. Increased inflammation in the brain as a result of COVID-19 leads to increased oxidative stress and damage to mitochondria [42].

It is well established that mitochondria have a pivotal role in ATP production, calcium hemostasis, the balance of oxidative factors, regulation of apoptosis, and neurotransmitter release in the axonal terminal. Mitochondrial dysfunction contributes to the pathogenesis of many diseases, including depression [43–48]. So, the dysfunction of mitochondria caused by COVID-19 may be a mechanism of COVID-19 induced depression.

Inflammatory cytokine exerts part of their neurodegenerative effects by disrupting mitochondrial axonal transport [49]. Kinesis and dynein are the motor proteins required for mitochondrial transport and are affected by the Coronavirus [50].

1.2.3. COVID-19, hippocampus disorder and depression

While the human coronavirus (HCoV) infection appears to spread rapidly throughout the CNS, it is more concentrated in the temporal lobe [51]. Several studies point out the vulnerability of the hippocampus to HCoV accompanied by a neuronal reduction in CA1 and CA3 areas and a detrimental effect on learning and spatial memory [52]. The specific vulnerability of the hippocampus to other respiratory virus infections, like the influenza virus, has been previously observed in mice [53]. In this study, the influenza virus alters hippocampal morphology and function and reduces hippocampal spatial memory and LTP. Even if the COVID-19 does not enter the CNS, severe hypoxia induced by respiratory system involvement can be enough to damage the hippocampus [54].

Depression induced by COVID-19 may exacerbate the hippocampus damage in COVID-19. Indeed, the hippocampus is the most interesting structure in the brain for studies related to depression. There are several reasons for this interest: 1. The hippocampus plays an essential role in memory and learning performance; so, its dysfunction may be the cause of inappropriate emotional responses (64). 2. The hippocampus is rich in corticosteroid receptors and has a close anatomical and physiological relationship with the hypothalamus stress axis through the axons of

the fornix, which sends regulatory (inhibitory) feedback to the HPA axis.

3. The hippocampus is one of the few areas in the brain with continuous neurogenesis in adulthood; hence, it has a high capacity to activate the process of neuroplasticity [55–61].

Studies have shown that depressive disorders are associated with a decrease in the number of neurons and glial cells as well as a decrease in the volume of some areas of the CNS, especially in the hippocampus [62,63]. A patient with a history of depression shows a significant reduction in hippocampal volume. The frequency and duration of depression periods are also associated with a reduction in the volume of the hippocampus [64].

Because MDD treated patients have a larger hippocampal volume than untreated, the clinical treatment appears to be associated with a return to normal structural changes [65,66]. Impairment of hippocampal synaptic plasticity and neurogenesis, as well as neurodegeneration and reduction of the volume of the hippocampus due to factors such as inflammation or neurotrophins reduction, contributes to the progression of the depression symptoms [67]. BDNF plays a key role in the growth, maturation, and survival of neurons and synaptic plasticity in the hippocampus. Stress reduces hippocampal BDNF and impairs neuronal survival [68]. The damaged hippocampus cannot adequately regulate (inhibit) the HPA axis allowing high cortisol levels to persist, which is likely to occur in COVID-19 infection disease [69,70]. Decreased hippocampal neurogenesis is another possible mechanism for the detrimental effects of proinflammatory cytokines. Neurogenesis has been implicated as a key contributing mechanism in the pathophysiology and treatment of depression [61,71,72].

1.3. COVID-19, malnutrition and depression

Clinical observations have shown that many patients with COVID-19 suffer from malnutrition. Some symptoms of COVID-19, such as dyspnea, anosmia, anorexia, dysphagia, nausea, vomiting, and diarrhea, are likely to lead to weight loss and malnutrition. SARS-CoV-2 can invade the epithelium of the oral mucosa and cause painful oral lesions and canker sores that significantly reduce nutrition in COVID-19 patients. Moreover, SARS-CoV-2 increases anxiety in patients, which reduces the patient's appetite and exacerbates malnutrition [73–75].

COVID-19 induced-malnutrition affects peripheral and central serotonergic pathways through tryptophan (TRP) deficiency (essential amino acid and serotonin precursor). Disruption of the serotonergic system (5-HT) plays an important role in a variety of psychiatric disorders such as depression and anxiety. Reduced TRP intake leads to decreased serotonin synthesis in the brain. Consumption of essential amino acids seems to increase the TRP / LNAA ratio. This ratio predicts the transfer of tryptophan through the blood–brain barrier to the CSF. Tryptophan is then used to synthesize brain serotonin, which reduces depressive symptoms. The consequences of malnutrition in the serotonergic pathways and depression have been proven [76,77].

1.4. COVID-19 vitamin D deficiency and depression

Malnutrition reduces the amount of essential vitamins in the body, which causes many neurological side effects such as depression. Some reports indicate that the level of vitamin D3, Zinc, and magnesium in blood serum are significantly related to depression. Vitamin D is one of the most important vitamins for normal CNS function [78,79]. The active form of vitamin D plays a protective role in the brain by decreasing the calcium concentration in neurons [80], and the vitamin D receptors (VDR) are detected in many parts of the brain. Vitamin D receptors are present in the hippocampus, and vitamin D deficiency is associated with a decrease in the hippocampus volume. Vitamin D also facilitates the production of serotonin in the brain [81–84].

Vitamin D can protect the neural progenitor of the hippocampus against the negative effects of glucocorticoids, which are high in chronic depression. Moreover, Vitamin D shows its neuroprotective effects in the hippocampus, mainly through its antioxidant and anti-inflammatory properties. Vitamin D3 also displays neuroprotection against calcium-induced neurotoxicity in the hippocampus. However, the exact effect of Vitamin D3 on BDNF is not fully understood [84–87]. An association between depression and vitamin D deficiency has been proven in many studies [81,82,88].

People with vitamin D deficiency are more prone to depression [80]. A meta-analysis study confirmed this relationship [89]. Magnesium is important for psychomotor function in major depression [90], and it is effective in the treatment of depression via glutamate [91], and some neurotransmitter systems [92]. Additionally, a negative relationship has been detected between zinc and depression [93].

There is a significant reverse relationship between the mean level of vitamin D and COVID-19 infections in European countries. Studies have shown a correlation between vitamin D levels and COVID-19 severity and mortality. The role of vitamin D in reducing acute viral respiratory tract infections and pneumonia through direct inhibition of virus replication or anti-inflammatory property has been established. Vitamin D supplementation has been shown to be safe and effective against acute respiratory infections. Therefore, people with vitamin D deficiency during the pandemic should consume vitamin D supplements to maintain an optimal blood concentration [75,94–96].

Vitamin D can be also useful in the correction of depression induced by COVID-19.

2. Conclusion

COVID-19 has emerged as a pandemic that may have long-term effects on human health. SARS-Cov-2 causes damage to various systems, including the respiratory, gastrointestinal, kidneys, and CNS. Among other common neurological symptoms, COVID-19 patients have also experienced depression. Depression and stress inducted by COVID-19 reduce the immune system and aggravate the infection. SARS-Cov-2 spreads directly and indirectly into the CNS, causes microglia over-activation, and produces inflammatory cytokines. A cytokine storm damages the BBB and exacerbates inflammation. This will ultimately cause apoptosis in various areas of the nervous system, especially the hippocampus. The severity of depression depends on the level of pro-inflammatory cytokines, particularly IL-6. Elevated cortisol levels, changes in the HPA axis, damage to the mitochondria, vitamin D3 deficiency, and malnutrition are some factors involved in the development of depression after infection with SARS-Cov-2. Understanding the mechanisms and factors involved in the development of depression in SARS-Cov-2 is an important factor in finding basic and appropriate therapeutic strategies for the treatment of infected patients.

Conflict of interest statement

There is no conflict of interest.

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