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SARS-CoV-2 consequences for mental health: neuroinflammatory pathways linking COVID-19 to anxiety and depression

Anna Julie de Mello, Morgana Moretti, Ana Lúcia S Rodrigues

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has been linked to an increased prevalence of mental health disorders, particularly anxiety and depression. Moreover, the COVID-19 pandemic has caused stress in people worldwide due to several factors, including fear of infection; social isolation; difficulty in adapting to new routines; lack of coping methods; high exposure to social media, misinformation, and fake reports; economic impact of the measures implemented to slow the contagion and concerns regarding the disease pathogenesis. COVID-19 patients have elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, and other inflammation-related factors. Furthermore, invasion of the central nervous system by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may potentially contribute to neuroinflammatory alterations in infected individuals. Neuroinflammation, a consequence of psychological stress due to the COVID-19 pandemic, may also play a role in the development of anxiety and depressive symptoms in the general population. Considering that neuroinflammation plays a significant role in the pathophysiology of depression and anxiety, this study investigated the effects of SARS-CoV-2 on mental health and focused on the impact of the COVID-19 pandemic on the neuroinflammatory pathways.

Key Words: Anxiety disorders; COVID-19 pandemic; Depression; Mental health; Neuroinflammation; Stress

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Core Tip: The COVID-19 pandemic has impacted the mental health of the population worldwide. This review summarizes the evidence of the role of neuroinflammation,

either as a result of chronic stress caused by the pandemic or SARS-CoV-2 infection, in the development of anxiety and depressive disorders.

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the coronavirus disease 2019 (COVID-19) as a pandemic[1]. More than two years have passed since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its ramifications have changed human lives worldwide. In response to the COVID-19 outbreak, the scientific community has collaborated to provide information on all aspects of the disease, including the devastating sequelae in survivors. The pandemic has directly affected people through infections and resulted in increased psychological stress in the general population.

Several factors contributed to the psychological consequences of the pandemic in the affected population, such as poor knowledge about the disease, previously undiagnosed mental health disorders, lack of a healthy lifestyle, no prior mental health assessment, economic problems, changes in eating and sleeping habits, difficulty in adapting to new routines, lack of coping methods, high exposure to social media, misinformation and fake reports, and social isolation during quarantine[2,3]. Quarantine and lockdowns have severely impacted everyday life worldwide, ranging from student education to the immense workload on health professionals[4]. Social distancing has isolated people inside their houses and significantly impacted the economy[5–7]. People with an infected household or a close contact with COVID-19 patients or those with a history of chronic illnesses have been shown to a higher risk of developing psychiatric distress[8,9].

Another concern is related to patients hospitalized due to COVID-19. Hospitalized patients are at risk of experiencing depression, anxiety, insomnia, and delirium[10]. Among all sequelae resulting from the disease, those of psychopathological nature can be induced either directly through the invasion of the virus in the central nervous system (CNS) or indirectly as a consequence of systemic inflammation and immune

response[11]. Neuroinflammatory alterations have been postulated to cause depression and anxiety[12]. Although there are several comprehensive literature reviews on the impact of SARS-CoV-2 on human health, in this minireview, we have discussed how neuroinflammation caused by chronic stress or SARS-CoV-2 infection can lead to anxiety and depression. We hypothesized that the neuroinvasion of SARS-CoV-2 in the brain, peripheral pro-inflammatory cytokines that may enter the brain after SARS-CoV-2 infection, and psychological stress associated with the pandemic, alone or in combination, could cause neuroinflammation and contribute to the development of anxiety and depression disorders.

COVID-19-RELATED STRESS AND THE HIGH PREVALENCE OF DEPRESSION AND ANXIETY

The increase in depression and anxiety during the COVID-19 pandemic has become a major health concern[2-4]. Depression and anxiety frequently co-occur and are prevalent and burdensome psychiatric disorders[13]. Depression was the second largest cause of disease burden in 2020[14–16] and has been projected to take precedence by 2030[17]. The most recent Atlas of Mental Health published by the WHO in 2020 revealed the indicators of mental health and Comprehensive Mental Health Action Plan, which has been extended till 2030 to assist individuals whose mental health has been affected by the COVID-19 pandemic[17]. Generally, anxiety disorders have a high annual prevalence at approximately 14%, with the United States and Europe presenting a higher rate than other areas[18,19]. One in four individuals is likely to develop or has already developed anxiety disorders[20]. Of note, the risk of developing anxiety and depression has been closely associated with exposure to chronic stress[21] such as that in the COVID-19 pandemic[22].

Coronaphobia, or excess anxiety about COVID-19, is strongly associated with elevated reports of depression, general anxiety, a lack of hope, and suicidal ideation[14,15,23]. A systematic review and meta-analysis of 13 studies with a total of 33,062 participants indicated a 23.2% and 22.8% prevalence of anxiety and depression,

respectively, in healthcare workers in China during the beginning of the pandemic, with a higher prevalence in female nurses[4]. In addition, the prevalence of depression and anxiety has increased in the general population, especially in young adults. During the initial stages of the COVID-19 pandemic in the United States, at least one-third of participants in a cross-sectional study reported high levels of depression (43.3%), anxiety (45.4%), and post-traumatic stress (31.8%)[24]. These rates were higher than those found in a previous study conducted in 2009 using the same assessment tools, showing a prevalence rate of 6.2% among young adults aged 18–24 years and 13.1% among those aged 25–34 years[25]. These symptoms were also associated with loneliness and low resilience to stress, whereas a higher tolerance to stress was associated with lower anxiety. Family support has been previously associated with lower levels of depression and post-traumatic stress disorder[24].

Another Chinese study conducted in 2020 reported a four times higher prevalence of depression, anxiety, or both, than a study published in 2019 (20.4% in 2020 vs. 4% in 2019)[26,27]. This study associated the development of depressive and anxiety symptoms with some common pandemic stressors, including worrying about oneself or loved ones being infected; concerns about income, jobs, school, and ability to pay loans; and hardships involving home quarantine in everyday life[26]. Depression and anxiety reported by Bangladeshi University students during the pandemic were associated with uncertainty about their academic or professional future and financial instability[28]. Early reports between mid-February and mid-March 2020 showed an increase of 34.1% in the demand for anxiolytic drugs, followed by 18.6% for antidepressants and 14.8% for sleep medications[29].

Studies on youth population have suggested that children and adolescents have also been affected by the pandemic. During the first year of the pandemic, one in four young adults experienced a clinical increase in depressive symptoms, with older children being the most affected. In addition, one in five children and adolescents had clinically elevated anxiety levels. The prevalence rates of depression and anxiety in children and adolescents increased over time and doubled compared to estimates before the

pandemic according to a recent meta-analysis[30]. Further, the global prevalence of depression and anxiety increased by 25% and 27.6% due to the COVID-19 pandemic in 2020, indicating the negative impact of COVID-19 on the mental health of people of all ages worldwide[31].

NEUROINFLAMMATION AND PSYCHOLOGICAL MANIFESTATIONS

Several studies have shown that inflammation plays a key role in the pathophysiology of depressive disorders[12]. Preclinical studies have provided consistent evidence that exposure of rodents to chronic unpredictable and/or inescapable stress situations induces depressive-like behavior accompanied by peripheral and central activation of the immune, inflammatory, and oxidative and nitrosative stress pathways. Furthermore, chronic administration of antidepressants attenuates these effects[32]. Chronic stress can also induce neurotoxic effects on specific brain regions, either directly or indirectly, through the kynurenine pathway[33], causing a reduction in brain-derived neurotrophic factor with consequent impairment of adult hippocampal neurogenesis[32].

Individuals with depression present with high serum levels of pro-inflammatory cytokines and acute-phase proteins and an increased expression of adhesion molecules and chemokines[34–38]. These protein alterations suggest an association between depression and activation of pro-inflammatory responses. Depression has been associated with increased levels of peripheral and central tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and C-reactive protein[34,37,39]. Furthermore, studies have reported an increase in the levels of other acute-phase proteins (i.e., α-1-acid glycoprotein, α-1-antichymotrypsin, and haptoglobin) in the plasma of patients with depression[37,40–42]. Elevated levels of human macrophage chemoattractant protein-1, soluble intracellular adhesion molecule-1, and E-selectin have also been reported[43]. An apparent association between the severity of depressive symptoms and level of inflammatory mediators in the plasma of patients has also been reported[34,44]. In addition, functional variants of alleles of IL-1β and TNF-α genes influence different

factors, either elevating the risk of depression or reducing the response to antidepressants[40,45,46].

Despite the frequent co-occurrence of anxiety and depression and their common association with cardiovascular[47] and metabolic diseases[48], the role of neuroinflammation in the pathophysiology of anxiety disorders has not been studied as extensively as that in depression[49]. Neuroinflammation may cause alterations in the structure or function of anxiety-related brain circuits (mainly the limbic and prefrontal regions), priming the brain to become vulnerable to anxiety disorders[33]. Studies have reported increased inflammation in patients of both sexes with late-onset anxiety disorder; however, they were unable to confirm it as an etiological factor[49]. Other studies have linked the immune system and CNS through key interactions that can influence behavioral changes; however, a causal relationship between anxiety and inflammation needs extensive investigation[49]. In preclinical studies, activation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome has been associated with anxiety-like behavior[50,51]. Clinical findings have suggested that increased cytokine levels affect neurotransmitters, such as monoamines and glutamate, in the amygdala, insula, and anterior cingulate cortex, which are brain regions related to anxiety[52]. Accordingly, inhibition of neuroinflammation has been accompanied by anxiolytic effects[51].

Increased levels of TNF-α, a cytokine important for cellular regulation and apoptosis, have been consistently associated with depression and anxiety in humans[53]. Similarly, central administration of TNF-α in mice resulted in depressive-like behavior, whereas TNF-α receptor 1 knockout mice exhibited antidepressant-like behavior in the forced swimming test and tail suspension test[54]. In addition, administration of TNF-α induced anxiolytic behavior in mice[55]. Administration of etanercept, a TNF-α blocker, reduced anxiety and depressive-like behavior in db/db mice exhibiting type-2 diabetes-related inflammation and mood alterations[56]. TNF-α blockade also caused an anxiolytic effect in mice with experimental autoimmune encephalomyelitis[55] and mice subjected to peripheral immune challenge with lipopolysaccharide[57]. Furthermore, administration

of the TNF-α-neutralizing antibody infliximab in the basolateral amygdala reversed anxiety-like behaviors in mice with persistent inflammatory pain[58].

During the initial phases of inflammation, IL-6 is induced along with TNF-α and may represent a key inflammatory mediator in patients with COVID-19[59–61]. Similarly, IL-1β is the major cytokine (in association with IL-18) produced by the activation of the NLRP3 inflammasome and increases in depression. These cytokines modulate the neuroimmune pathways that regulate critical brain circuits involved in cognition, mood, and reward[62–64]. Notably, SARS-CoV-2 is postulated to directly activate the NLRP3 inflammasome, and patients with dysregulated NLRP3 inflammasome activity may develop COVID-19 with severe tissue damage and a cytokine storm[65].

Increased levels of pro-inflammatory cytokines such as IL-6 may repress brain-derived neurotrophic factor, contributing to the development of depressive behavior[66,67]. IL-6 is also associated with lymphocyte exhaustion, and its role in COVID-19 inflammation has propelled the use of IL-6 inhibitors, corticosteroids, antimalarial drugs, and intravenous immunoglobulin to oppose the effects of cytokine storms in individuals with COVID-19[68]. Therefore, a strong inflammatory response can be related to disease severity and death in patients with COVID-19[68]. In severely affected patients, increased levels of peripheral cytokines can cause lymphopenia and invasion of mononuclear cells in the heart, lungs, lymph nodes, spleen, and kidneys[69]. A study on COVID-19 survivors revealed elevated depression, anxiety, insomnia, post-traumatic stress disorder, and obsessive–compulsive symptoms one month after hospitalization[70]. These findings are consistent with those reported during the previous coronavirus outbreaks, in which 10%-35% patients in the post-disease recovery stage presented psychiatric comorbidities[10]. These psychiatric outcomes may be a consequence of neuroinflammation caused by COVID-19. Moreover, neuroimaging and CSF marker elevations in patients with COVID-19 have suggested that SARS-COV-2 causes CNS inflammation[71].

NEUROINVASION BY SARS-COV-2

Individuals infected with SARS-CoV-2 can remain asymptomatic or develop COVID-19 symptoms. Hospitalized patients with COVID-19 commonly present with clinical sequelae that appear up to three months after discharge[72]. These sequelae are not limited to respiratory issues because patients can manifest cardiovascular, neurological, and psychosocial symptoms after discharge[11,72,73].

The neurological symptoms after COVID-19 may be associated with direct SARS-CoV-2 invasion of the CNS, where the virus has a high potential for replication, causing significant neuronal death[74]. Patient autopsies have revealed neuronal loss[75], often associated with an immune response against the virus in the CSF. Few reports showed that patients who tested positive for SARS-CoV-2 in their CSF but did not have any significant risk factors or a history of neurological diseases manifested neurological symptoms, such as seizures and loss of consciousness[76].

Most *in vitro* and *in vivo* experiments support the hypothesis that neuroinvasion by SARS-CoV-2 causes neurological symptoms in patients with COVID-19. The presence of the virus within neurons in multiple brain areas of infected animals resulted in a neuropathology similar to that observed in hospitalized patients[77]. Importantly, these alterations are not limited to adult patients; children also manifest the same critical developments after COVID-19, including thrombosis, inflammation, and secondary tissue ischemia[78,79]. Severe COVID-19 is rarely reported in children; however, there have been reports of children who developed acute fulminant cerebral edema, severe encephalopathy, and ischemic stroke despite being previously healthy[80,81].

Animal experiments have provided detailed information regarding the neuroinvasive potential of SARS-CoV-2. A study by Song *et al.* revealed that SARS-CoV-2 infects animal lungs at early time points, while it infects the brain much later[74]. In the same study, electron microscopy to identify viral particles sprouting from the endoplasmic reticulum indicated that the virus could use cellular machinery for replication. Unlike other neurotropic viruses such as Zika, SARS-CoV-2 causes metabolic changes in the brain, as demonstrated using human brain organoids[74].

The literature further suggests SARS-CoV-2 neuroinvasion occurs through the trans-neuronal route, especially during the early stages of infection, in which SARS-CoV-2 invades the brain *via* the cranial nerve pathways such as the olfactory, gustatory, and trigeminal nerves[77]. This infiltration route is also associated with the severity of infection and neurological manifestations that lead to a higher risk of mortality in patients with COVID-19. Liu *et al* reported that death occurred only in infected animals with neurological deficits, suggesting that disease progression is associated with the severity of neurological involvement[77].

Involvement of the trans-neuronal route suggests that SARS-CoV-2 enters the CNS through the olfactory nerves *via* angiotensin-converting enzyme 2 (ACE2; a part of the renin-angiotensin-aldosterone system) present on the cell membrane. The virus then migrates through the neuroepithelium and reaches the brain, consistent with the loss of smell observed in patients with COVID-19[82,83]. This route of SARS-CoV-2 neuroinvasion has been demonstrated by Song *et al* in mice overexpressing human ACE2[74]. Accordingly, COVID-19 respiratory distress has been associated with increased nasopharyngeal expression of ACE2 and transmembrane serine protease 2[84]. In addition, clinical studies and *post-mortem* analyses have reported the presence of viral antigens in the olfactory tract[85–88]. Magnetic resonance imaging examination of patients with COVID-19 revealed structural changes throughout the olfactory pathway, including the nerve, bulb, and cerebral cortex, and supports the olfactory bulb route hypothesis[83,89,90]. Immunostaining for SARS-CoV-2 in animal models has revealed extensive staining in these regions[91,92].

Another plausible entry route for SARS-CoV-2 could be through the blood-brain barrier (BBB) by binding to ACE2 on endothelial cells[82]. This route, previously linked to infected individuals with high fever, may cause cytokine storms and increase the BBB permeability[93,94], thereby facilitating the access of SARS-CoV-2 to the brain[95]. As a consequence of BBB impairment, peripheral immune cells can enter the brain, increase the release of pro-inflammatory cytokines by microglial cells and sustain neuroinflammation[96].

Finally, *post-mortem* studies have reported the presence of ischemic damage and microinfarcts in brain samples of patients with COVID-19, supporting the assumption of SARS-CoV-2 neuroinvasion into the CNS[74].

CONCLUSION

As illustrated in Figure 1, the increased prevalence of depression and anxiety during the COVID-19 pandemic may be attributed to SARS-CoV-2 neuroinvasion and its harmful consequences on the CNS. Depression and anxiety may also occur because of peripheral inflammation caused by the virus and indirect negative effects on the brain function. Moreover, long-lasting social stressors linked to the pandemic may contribute to neuroinflammation and, consequently, to the development of these psychiatric symptoms. Therefore, anxiety and depression can affect the infected individuals and general population exposed to long-lasting pandemic stress. In the future, epidemiological studies should be conducted to elucidate the COVID-19 psychiatric burden, and public health control measures to help manage this burden must be provided.

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