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Short communication

The potential impact of Covid-19 on CNS and psychiatric sequels

Ali Dehghani a, Elham Zokaei b, Seyyed Mohammad Kahani a, Elaheh Alavinejad c, Mohammad Dehghani d, Gholam Hossein Meftahi e, Mohammad Reza Afarinesh f,g,1

a Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
b Department of Biology, Faculty of Science, Shahid Beheshti University of Kerman, Kerman, Iran
c Department of Medical Genetics, Faculty of Medical Sciences, Tehran University of Medical Science, Tehran, Iran
d Department of Pathology and Stem Cell Research Center, Kerman University of Medical Sciences, Kerman, Iran
e Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
f Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

Due to its high prevalence and fatality, the current Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) virus, which first emerged in China in 2019, quickly spread around the world and immediately became a serious global health concern. Although respiratory issues were initially the most prominent symptom of coronavirus disease 2019 (COVID-19), it became obvious rapidly that COVID-19, like many other coronavirus family members, could affect the central nervous system (CNS). During the pandemic, CNS involvement expressed itself in a variety of forms, including insomnia, anosmia, headaches, encephalopathies, encephalitis, cerebrovascular accidents, cognitive and memory impairment, and increased psychiatric disorders. Almost everyone who has been infected has at least one of these neurological symptoms, demonstrating that the virus has a high ability to impact the CNS. As the coronavirus pandemic passes its second year, the manifestations it can cause in the long run, such as its psychological sequels, have not yet been thoroughly studied. Given the high importance of this issue in today’s society and due to the lack of reliable knowledge about the COVID-19 landscape on psychiatric disorders, we intend to investigate coronavirus’s possible effect on mental illnesses based on available literature. Because the majority of the psychological effects of the coronavirus can continue for a long period after the pandemic ends, our research can give insight into potential psychiatric sequelae associated with COVID-19.

1. Introduction

Coronaviruses are a category of large-enveloped non-segmented positive-sense RNA viruses that generally target the human respiratory system, but they can also migrate to the central nervous system (CNS) and operate as neuroinvasive agents. The intensity of the symptoms can vary greatly, and they can affect humans as well as a variety of animal species (Pennisi et al., 2020). Two novel coronavirus strains with high morbidity and fatality rates have caused serious disease in humans over the last two decades: acute respiratory syndrome coronavirus 1 (SARS-CoV-1) in 2002 and the middle east respiratory syndrome coronavirus (MERS-CoV) in 2012 (Khateb et al., 2020).

At the beginning of December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in China and soon after that, became a worldwide pandemic (Morgello, 2020). The clinical manifestations of SARS-CoV-2 infection range from fever, cough, dyspnea, and fatigue to acute respiratory distress syndrome, acute cardiac problems, and multiorgan failure (Harapan and Yoo, 2021). Coronavirus infections have been linked to neurological manifestations (e.g., febrile seizures, convulsions, mental status changes, encephalitis, encephalomyelitis, and demyelination), indicating that they may have neurotropic properties. Coronavirus’s neurotropic and neuroinvasive capacities have been proven without a shadow of a doubt (Liu et al., 2021; Zubair et al., 2020). For example, upon intranasal infection, coronavirus can invade the CNS through the olfactory bulb, inducing neurological dysfunction (Chiu et al., 2021; Liu et al., 2021; Meinhardt et al., 2021). COVID-19 RNA was found in the CNS of 48% of the study participants in one post-mortem research (Meinhardt et al., 2021). COVID-19 is progressively being reported to impact the structure, function, metabolism, and activity of the frontal and temporal lobes, and in several T2-weighted MRI investigations, COVID-19 patients showed white matter

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hyperintensity in the frontal cortical region/right frontal lobe/right prefrontal cortex (Duan et al., 2021; Kaya et al., 2020). Furthermore, COVID-19 individuals also had hypodensity in white matter and gray matter in the right/posterior frontal gyri, as well as symmetric bilateral hypodensity in the temporal area, according to CT head imaging studies. Unfortunately, all these abnormalities are likely to persist even after recovery from COVID-19 (Duan et al., 2021; Goel et al., 2020; Princiotta Cariddi et al., 2020).

The rising occurrence of various psychiatric morbidities during the pandemic suggests that coronavirus may play a role in psychiatric disorders such as depression, adjustment reactions, psychotic symptoms, post-traumatic stress disorder (PTSD), and even greater suicidality (Khteb et al., 2020). Since the pandemic passed its second year, the medium and long-term consequences are coming into attention. At the top of the list of priorities is psychiatric disorders.

To answer the question of how much the coronavirus is associated with mental illness, we screened the all-available literature regarding probable psychiatric sequels of recent coronavirus infection to clear the COVID-19 relationship with psychiatric disorders.

2. COVID-19 and nervous system

SARS-CoV-2, like other mammalian coronaviruses, has a well-documented ability to infect the CNS. The virus first infects peripheral nerve terminals before making its way to the CNS via a trans-synaptic transfer (Morgello, 2020; Nagu et al., 2021). The human OC43 CoV and the swine hemagglutinating encephalomyelitis virus (HEV), which infects the porcine brain via retrograde neural propagation through the peripheral nerves, have a 91% similarity, according to Andries and Pensaert, 1980). The detection of COVID-19 RNA and protein particles in CNS specimens, including fluid or parenchyma and brain tissue edema, as well as partial neuronal degeneration in deceased individuals due to respiratory failure, can indicate the possibility of SARS-CoV-2 directly infecting the neurological system (Soltani Zhangbar et al., 2021). SARS-CoV-2 can infect tissues via connecting to the angiotensin-converting enzyme 2 (ACE2) receptor on particular host cells, according to new research (Bahari et al., 2021; Meftahi et al., 2020). This binding, like that of SARS-CoV, is mediated by the spike protein found on the surface of SARS-CoV-2. However, with a 20-fold increase in binding affinity (Wrapp et al., 2020). According to a series of studies from China and France, up to 84% of COVID-19 hospitalized patients have neurological symptoms (Helms et al., 2020; Morrow et al., 2018). Following the report of a COVID-19 patient who lost involuntary control of breathing due to suspected involvement of the inspiratory area in the brainstem, as well as numerous patient reports of anosmia, insomnia, and convulsions, the possibility of significant COVID-19 neurological deficits became a concern (Baig, 2020; Uversky et al., 2021). COVID-19 neurological symptoms are divided into two categories: mild and severe. Headaches were reported by nearly 53% of COVID-19 patients (Bodro et al., 2021; Guan et al., 2020). Although the headaches were mainly described as mild, a few patients complained of a severe form (Gupta et al., 2020). Headache is a common clinical symptom of a variety of neurological illnesses, including meningitis, encephalopathies, encephalitis, intracranial hypertension, cerebrovascular diseases, and vasculitis, all of which have been linked to COVID-19 by some pathology findings (Bobbek and Robbins, 2020). Moreover, dizziness and gait imbalance were reported in 7.7% and 5.0% of COVID-19 patients, respectively (Agarwal et al., 2021). There may be a relationship between the coronavirus family and demyelinating diseases such as multiple sclerosis (Gusev et al., 2021). It was discovered that the S gene of the coronavirus mouse hepatitis virus, which is very similar to human coronavirus, is related to specific molecular aspects of demyelination, indicating a potential role of viral envelope S glycoproteins in autoimmune-induced demyelination (Sarma et al., 2000). Acute necrotizing hemorrhagic encephalopathy is an uncommon encephalopathy produced by intracranial cytokine storms that result in a breach of the blood-brain barrier. It has been linked to other viral infections such as influenza, but has yet to be linked to the COVID-19 infection. The COVID-19 patient has also been diagnosed with cytokine storm syndrome (Adamczyk-Sowa et al., 2021; Demirci Oluoglu et al., 2020). COVID-19 caused acute hemorrhagic necrotizing encephalopathy in a 58-year-old woman, according to Poyiadjis et al. (2020). Cranial magnetic resonance imaging of their case showed hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions (Poyiadjis et al., 2020). Furthermore, thrombosis is more likely as a result of cytokine storms generated by coronavirus infection. Moreover, elevated platelet count and D-dimer test results have been observed in SARS-Cov-2 infection, implying a probable relationship between recent SARS-Cov-2 infection and acute ischemic stroke (Zhang et al., 2021). Acute flaccid paralysis (AFP) is a life-threatening neurological disorder marked by severe weakening or paralysis, as well as diminished muscle tone, particularly in the respiratory and bulbar muscles, due to injury to lower motor neurons. A 66-year-old man with COVID-19 was admitted with AFP of bilateral lower limbs, as well as urine and bowel incontinence, which developed about a week after a fever and subsequent respiratory symptoms (Zhao et al., 2020b). When it comes to peripheral neuropathies, the syndrome is usually a manifestation of Gullian–Barre syndrome (GBS). A 61-year-old man was diagnosed with an acute inflammatory demyelinating polyneuropathy (AIDP) subtype of GBS linked to SARS-CoV-2 was reported in the Zhao et al. (2020) study (Zhao et al., 2020a). Another study described a 70-year-old woman who developed moderate respiratory symptoms after contracting COVID-19, followed by a rapidly progressing quadriplegia, implying that SARS-CoV-2-induced GBS was the cause (El Otmani et al., 2020).

To summarize, all of the evidence points to COVID-19’s ability to enter the CNS, as well as the possibility that the invasion may entail multiple mechanisms.
2.1. Cognitive and memory impairments

Dementia and cognitive decline are prevalent symptoms among COVID-19 patients (Zhou et al., 2021). Previous research on viruses such as the cytomegalovirus and the herpes simplex virus has found a link between dementia and virus infection (Warren-Gash et al., 2019). Besides, histological examination of HCOV-OC43 infected mice has shown a smaller hippocampus than the non-infected ones (Jacomy et al., 2006). The hippocampus appears to play a substantial role in long-term episodic memory (Bird and Burgess, 2008).

As previously stated, dendrites and extend axons of olfactory nerves provide a shortcut for virus entry into the brain through the nasal cavity (Zhou et al., 2020). Based on anatomical and electrophysiological studies, there is a link between the hippocampus, amygdala, and olfactory nerves. Moreover, memory for environmental odors is a vital part of a wide range of animals’ lives and it can reveal the evolution of a link between memory-related regions and olfactory neurons. Dahmani and her colleagues have shown a correlation between olfactory identification and spatial memory in humans (Dahmani et al., 2018; Mouly and Sullivan, 2010). Therefore, according to the mentioned evidence, viruses can enter memory-related areas of the brain via olfactory nerves and influence the memory process. The second primary pathway for SARS-CoV-2 neuroinvasion is through binding to ACE2 and infected monocytes and macrophages (Rizzo and Paolillo, 2021). The transmembrane protein ACE2 is found in both neurons and glia. The hypothalamic area, as seen in post-mortem human brain tissue and transgenic mice, is a strong source of ACE2. Hypothalamic signals have long been recognized as an important channel in the learning and memory processes. According to studies, the SARS-CoV-2 virus can enter neuron cells by attaching to ACE receptors. After COVID-19 infection, downregulation of ACE2 receptors and, as a result, an imbalance of ACE/ACE2 activity occurs, causing or exacerbating neurological impairment (Burdakov and Peleg-Raibstein, 2020; Iwasaki et al., 2021; Rizzo and Paolillo, 2021). Furthermore, according to recent research, coronavirus-induced neuroinflammatory processes pave the way for memory and cognitive impairment. According to Kenny and his colleagues’ survey, there are various types of inflammatory factors in the cerebrospinal fluid of dementia patients, which show an association between immune system activity and memory decline (Kinney et al., 2018). Uprogulation of pro-inflammatory cytokines increases the production of cyclooxygenase-2 (COX-2) and the activation of matrix metalloprotease (MMP), resulting in blood-brain barrier (BBB) breakdown. More viruses and inflammatory mediators enter the CNS in the next step, which is followed by the permeable BBB. Overall, microglial activation and oxidative stress caused by cytokines result in synergistic cognitive impairment towards the end of this cascade (Baker et al., 2021).

Severe COVID-19 infection can result in hypoxia and brain damage, which can have a negative impact on mental health (Schultz et al., 2018). The majority of acute respiratory distress syndrome (ARDS) survivors have complained and reported cognitive impairment, hallucination, and limited or loss of memory (Hopkins et al., 1999). A significant number of inpatients with severe COVID-19 needed mechanical ventilation. Considering previous neurological evidence, neurological deterioration such as memory impairment, difficulties with attention, and verbal impairment has been observed as a consequence of ventilated patients (Ritchie et al., 2020; Vannorsdall and Oh, 2021).

Confinement during the COVID-19 period imposes a limitation on communication between friends and family, leading to increased anxiety, depression, and stress. All of those consequences of isolation can have detrimental impacts on cognitive decline (Barguilla et al., 2020; Vannorsdall and Oh, 2021).

To summarize, all of the aforementioned factors, including the entry of SARS-CoV-2 into the brain and subsequent changes such as inflammatory molecules derived from infection, PTSD, ARDS, and isolation during the coronavirus outbreak, resulted in cognitive impairments or worsened pre-existing problems. There are some noticeable limitations in the evaluation of the memory and cognitive changes related to the current coronavirus epidemic. First of all, an unknown number of infected cases have no signs of neurological disorders, as well as no exact statistical data about the whole number of exposed people to the virus. The amount of research and surveys that confirm the link between cognitive changes, dementia, and infection is the second big hurdle to generalizing these symptoms to the general population (Ritchie et al., 2020; Vannorsdall and Oh, 2021). Therefore, we recommend a detailed investigation into the relationship between the severity and period of infection and the level of cognitive and memory decline in the short and long term.

2.2. Stress-related disorder

The current pandemic is associated with a variety of stressors. Bad news on a daily basis, such as extremely high prevalence and mutation of the virus, an increasing number of deaths, the spread of wrong information and rumors in the rest of society, and extreme pressure regulators like quarantine, self-isolation, loss of work, family conflicts, or grief of losing loved ones, are among the main stressors associated with the COVID-19 pandemic (Qi et al., 2016). Given the psychological burden during the COVID-19 pandemic, the relationships between the mounting risk and flexibility factors, stressors, and stress-related symptoms should be investigated. Recent preliminary research has demonstrated that both frontline medical staff and the public are experiencing a range of psychological problems, including stress-related disturbances, anxiety, and depression (Annett et al., 2020; Salehi et al., 2021). Symptoms of adjustment disorder (AD) or PTSD were most often reported (Dragan et al., 2021; Rossi et al., 2020). Therefore, COVID-19’s appearance and its rapid spread increased stress and anxiety in communities around the world, creating an emergency that led to mental health problems in individuals.

To begin with, PTSD is a complex mental disorder with psychological and emotional components caused by exposure to single or repeated extreme traumatic events. PTSD symptoms may come in the form of intrusive thoughts, avoiding reminders of intrusive memories, negative thoughts, and feelings, as well as exaggerated reactions and symptoms. These can cause crucial and notable distress and problems (Fenster et al., 2018; Raudenska et al., 2020; Salehi et al., 2021). Another most likely consequence of the stress of pandemics on mental health would be AD, which appears in the response to stressors associated with disasters. AD is a condition of internal distress and emotional disturbance that interferes with social or professional functioning and that arises during a period of adaptation to an adverse life change or life event (Dragan et al., 2021; Mahat-Shamir et al., 2017; Zelviene and Kazlauskas, 2018). The main distinction between AD and PTSD is the severity of the stressful event, which can result in qualitatively different stress responses. Stressors linked to PTSD are usually more intense than traumatic events in the case of AD, in terms of having a sudden and unexpected threat to human life. However, both create serious conditions for individuals that should not be neglected. These mental disorders could be present in the several months since the start of the outbreak and could last long after the vaccine or effective medication to treat patients becomes available (Maercker et al., 2007; Mahat-Shamir et al., 2017). Hence, even after COVID-19 is eradicated, uncertainty about the future, as well as feelings of anxiety and fear, may continue to be prevalent.

Providers can predict a raised incidence of stress-related disorders in COVID-19 survivors based on the cohort and research information from human coronavirus outbreaks in the past, despite differences between them (Kaseda and Levine, 2020). As an example, one year after the MERS outbreak, 42% of all survivors had PTSD, chronic fatigue, and depressive symptoms that were above the clinical cut-off, and just under two-thirds of them remained above the cut-off after 18 months (Lee et al., 2019). Likewise, in the wake of the SARS outbreak, in 2003, after 30 months of SARS outbreaks almost 26% of survivors experienced full
PTSD, and all recognized SARS infection as the cause of their trauma (Mak et al., 2010). Moreover, a four-year follow-up study of 70 survivors of SARS, found that 44% developed PTSD. Even after recovering from SARS, PTSD persisted for years in almost all (82%) of these sufferers. The appearance of stress-related symptoms was more significant among the related-hospital workers in Beijing, China, even after three years of the SARS outbreak (Wu et al., 2009). These prevalence rates were much higher than the population average, implying that clinicians should be prepared to assess and make suggestions regarding elevated PTSD in similar circumstances.

During the COVID-19 pandemic, existing studies have shown variation in the prevalence rates of stress-related disturbances. Using different methods of estimation and assessment tools, variation in sample size makes direct comparisons impossible. Furthermore, most of the current studies are based on web-related recruitment and voluntary participation through social networks, so it is highly likely the selection underwent some unbalanced gender ratio (higher proportion of females) or excluding many people not on social media like the elderly or could not participate due to multiple obligations at home and work (Mathur et al., 2020). However, most of the findings confirm that gender (female) and employment postural instability medication, living alone, and being posted in the COVID19 section in hospitals are significant risk aspects associated with a high risk of developing subjective distress and PTSD (Dutheil et al., 2021). Hence, these cases should be taken into consideration when making social and health policies (Li et al., 2020a; Mathur et al., 2020).

According to a web-based survey directed by Rossi et al. (2020), with 79.6% of women participants, the rate of different mental health outcomes was assessed in the Italian general population during the 10 days of the first phase of the COVID-19 pandemic. Almost a quarter (23%) of respondents reported symptoms of AD. For other outcomes, 37% reported PTSD, 22% high perceived stress, 21% anxiety, and 17% depression. Being female and being younger in age were associated with all the mental distress outcomes (Rossi et al., 2020). At the same time, the prevalence and severity of the symptoms of AD, PTSD, depression, and generalized anxiety in a large sample of adult Poles recruited through the web were (14%, (2.4%), (26%), and (44%), respectively (Dutheil et al., 2021). According to Mathur S. and et al., (2021), in an Indian population of front-line workers, 9.5% of respondents experienced acute stress, 17% experienced depression, and 19.5% experienced anxiety (Dutheil et al., 2021; Mathur et al., 2020). Whereas Lai J. et al. (2020) found a prevalence of 50.4% for depression, 44.6% for anxiety, and 71.5% for distress, Tan BYQ et al. (2020) found a prevalence of 8.1%, 10.8%, and 6.4% for depression, anxiety, and stress in medical healthcare personnel (Lai et al., 2020; Tan et al., 2020). Two surveys conducted by Wang Y. and et al., (2021) between January 31 and February 2, and February 28 to March 1, 2020, predict 8.1% moderate-to-severe stress, 28.8% anxiety, and 16.5% depression (Wang et al., 2021). COVID-19 causes not only physical health problems but also a variety of psychiatric conditions in various cultures. During the COVID-19 pandemic, it is critical to maintain individual mental health and establish therapeutic approaches that can enhance vulnerable groups’ mental health.

There is mounting evidence demonstrating two phases of the response model to stress related to disturbances: acute stress and chronic stress, where there is a thin line between them. While the former may enhance the immune response, the chronic one may reflect a reverse response, a decreased in the immune response, as it creates hyper-sensitivity to the infection. The research indicates that suppression and strengthening of the immune response can be seen simultaneously by changing the pattern of cytokine expression, which generates both short-term and long-term stress-related symptoms (Li et al., 2020b; McEwen, 2017). On the other hand, observations show that patients with chronic stress, particularly vulnerable people such as the elderly, pregnant women, or those with chronic diseases who are more likely to be treated with immunosuppressants, are more likely to suffer from a weakened immune system and a greater vulnerability to contracting life-threatening and lethal viral infections as a result of such infections. Similarly, in the case of the Covid-19 pandemic, psychological problems that are above average weaken the body’s immune system and consequently increase the risk of catching the virus. During the stressful and tense period of pandemics, and with the high prevalence proportion of mental disturbances, far above the population average, the significance of psychological service from the early stage should not be negligible.

Emergency interventions should be implemented among people to reduce the consequences of stress-related disorders and alleviate the incidence of chronic stress, which leads to preventing immunosuppression, thus breaking the vicious circle (Li et al., 2020b; Lotzin et al., 2020; McEwen, 2017; Song et al., 2018). Moreover, identifying the critical factors contributing to developing stress symptoms is crucial for prioritizing the more susceptible and vulnerable groups. Following the critical period of the COVID-19 pandemic, evidence suggested that those who survived the deaths were healthcare professionals, particularly those with overworked and low safety equipment, healthy people who were directly exposed to the infection, and people who were highly and steadily exposed to restrictive measures such as social distancing, quarantine, isolation, or being exposed daily to too much bad news (Islam et al., 2020; Li et al., 2021). In this regard, investigating the intersection of chronic stress, which leads to epidemic burnout rates among frontline workers and the general population, and acute traumatic stress imposed by outbreaks is serious and necessary in order to inform interventions (Qi et al., 2016).

2.3. Sleep problems

Insomnia and other sleep disorders are major health issues associated with great psychological and physical pressure. Complicated interconnections between neurotransmitters, immunologically active peptides, and hormones regulate sleep function, which is considered an essential phenomenon of the CNS (Lange et al., 2010). Stress levels and changes in sleep behaviors are two main contributors to potential arousal and disturbed sleep. The evidence demonstrates that poor sleep quality and psychological distress symptoms are intractably intertwined (Ibarra-Coronado et al., 2015). Therefore, there is a bidirectional association between sleep issues and psychiatric comorbidities like anxiety and depression, as well as stress-related disorders, implying that sleep therapists should address psychiatric comorbidities when treating sleep problems, and vice versa (Ibarra-Coronado et al., 2015; Jahrami et al., 2021).

Worried about getting an infection or other issues that might not be optimally addressed, namely financial trouble, as well as other psychological issues, can be attributable factors to creating a situation with a high level of stress, hence leading to abnormal sleep schedules (Altena et al., 2020). Physical pain and side effects of medications administered for the treatment of the infection, as well as a high risk of sleep problems among patients with COVID-19 worldwide, are reported (Altena et al., 2020; Jahrami et al., 2021; Leen et al., n.d.). Furthermore, most confinement studies are not like the existing COVID-19 pandemic-related confinement situation. Loneliness and confinement in quarantine because of changes in the environment, light exposure, diet, and environmental temperature may affect psychological well-being and induce a sense of vulnerability, affecting the quality of sleep. On the other hand, poor sleep quality creates a feeling of frustration and isolation. Individuals’ contacts with others may be disrupted due to an irregular sleep-wake schedule (Altena et al., 2020; Ashkanami et al., 2021; Leen et al., n.d.; Potter et al., 2016). As a result, limiting tension and probably preventing social relationship disturbances during home confinement can be accomplished by managing sleep issues as best as possible.

Having said that, however, most investigations suggest that the psychological effects of confinement during COVID-19 outbreaks are not the basic and specific factors for sleep questionnaires. Instead, they have mostly focused on frontline health workers (nurses and physicians...
exposed directly to infection) or general people who have suffered from the virus or been exposed to it, with a usually confined period of two weeks (Brooks et al., 2020; Goyal et al., 2021). A summary conducted by Jahrami et al. (2021) assessed the impact of the COVID-19 pandemic on the prevalence and severity of sleep problems among the general population, health care workers, or patients with COVID-19. These investigations indicate an extremely high pooled prevalence rate of disturbing sleep patterns globally, which affects roughly 40% of the population in general and health, care workers. Patients infected with COVID-19 emerged to have the highest frequency of disturbed sleep, with an average rate of 74.8%. One might argue that this may happen because the primary symptoms of the disease, including coughing, fever, and respiratory problems, have all been associated with sleep disorders (Jahrami et al., 2021). However, before larger, better-designed studies are available, it is critical to take this finding seriously.

However, further important findings show that sleep is not simply a period in which activity and alertness decline. It is a vital process that modulates various physiological functions (Kryger et al., 2005). The interaction between sleep problems and the COVID-19 pandemic is not yet completely clarified. Sleep and the immune system, according to researchers, interact bidirectionally. This hypothesis is supported by altered sleep patterns during viral infections, particularly in the acute phase of the immune response and the development of recovery during sickness, similarly through mechanisms that involve cytokines and interleukins and their receptors, as well as receptors of the innate immune system. The response of the immune system to infection and, as a result, the release of these immunological mediators is associated with responses by the endocrine and nervous systems, such as the secretion of cortisol and epinephrine. These substances can cross the BBB to reach their receptors in various neural structures or may have vagal input to modulate the responses that maintain homeostasis (Altena et al., 2020; Ibarra-Coronado et al., 2015; Jahrami et al., 2021). Given this information, further studies would be urgently needed to reach a comprehensive understanding of the relationship between the neurological pathology of COVID-19 and the nervous system. The most comprehensive knowledge about the interaction between sleep disorders and the potential virus, the better and faster-improved sleep quality, resulting in greater mental and psychiatric health in both the general population and health care workers during pandemics.

2.4. Major depression

Major depressive disorder (MDD) is a prevalent chronic psychiatric condition that seems to have a negative impact on one’s emotions, thinking, and physical well-being. It is also related to feelings of guilt, aversion to activity, insomnia, and reduced motivation or ability to experience pleasure (anhedonia) (Kato et al., 2020; Liu et al., 2020; Pu et al., 2020; Shields et al., 2021). COVID-19 may have influenced MDD in a variety of ways, including immunological response, infection, and social isolation (Borges et al., 2020; Guo et al., 2021; Yuan et al., 2020). COVID-19 infection through the immune response, hyper inflammation, and social isolation may lead to high depression disorder or worsen MDD in patients suffering from depression.

In a severe COVID-19 infection, innate immune cells such as monocytes can cause excessive inflammation in the immune response pathway. These cells express pattern recognition receptors such as toll-like receptors, which normally protect the body from viral infections. When pattern-associated molecular patterns of the virus are identified, the NF-B pathway is activated, and the COVID-19 induced cytokine storm produces cytokines such as interleukin (IL-1), tumor necrosis factor-alpha (TNF-α), and IL-6. Furthermore, in contrast to SARS and MERS patients, levels of T-helper-2 cell-secreted cytokines (such as IL-4 and IL-10) are elevated, suggesting that these variables are dysregulated and elevated in MDD patients (Mazza et al., 2020). Additionally, some studies demonstrate that depression is linked to an increase in inflammatory and immune markers such as C-reactive protein (CRP) and pro-inflammatory cytokines like IL-6. Similarly, some studies show an elevated level of IL1, IL6, TNF-α, CRP in MDD patients (Choi et al., 2021; Yuan et al., 2020). Although cytokines are a crucial part of the inner immune system that protects against viral infection, COVID-19 can cause a psychiatric condition by triggering a “cytokine storm” (Meltahil et al., 2021). It is hypothesized that dysregulation of cytokines affects MDD because cytokines play a vital role in the process of behavior and emotion in certain brain regions. Most studies have found that the amount of IL-6 in the CNS and plasma plays a pivotal role in depression (Shields et al., 2021; Steardo and Verkhratsky, 2020). As a result, despite the beneficial role of cytokines in protecting against COVID-19 infection, cytokine storm-induced hyperinflammation may lead to depression or exacerbate pre-existing depression.

In another way for COVID-19 to cause hyperinflammation, the virus can attach with its spike to the ACE2 receptor and enter the alveoli cells with the receptors; as a result, the levels of ACE2 receptors are reduced, causing high levels of angiotensin II (which has anti-inflammatory properties), and inflammation is increased as a result of these events. Hyperinflammation can arise in various organs, notably the CNS, because ACE2 receptors are expressed in the gastrointestinal system, heart, kidney, endothelium, and CNS (Adu et al., 2021; Harrison et al., 2020). Therefore, the entry of COVID-19 into the CNS via the ACE2 pathway and subsequent inflammation can play a significant role in the development of MDD.

Depression in COVID-19 patients is probably due to downregulation of the hypothalamic–pituitary–adrenal axis (HPA) and a reduction in serotonin biosynthesis, two probable reasons for depression. As a result of the high inflammation generated by COVID infection, tryptophan enters the kynurenine pathway, changing the tryptophan vs kynurenine ratio and affecting serotonin levels, which has been linked to a variety of conditions, including neuropsychiatric disorders (Vyavahare et al., 2021). Changes in serotonin uptake in various areas of the brain (such as the amygdala) have been linked to depression (Vyavahare et al., 2021). Furthermore, the HPA axis pathway’s feedback mechanism is disrupted by diminished glucocorticoid receptor sensitivity caused by excessive inflammation. As a result, it promotes hyper-activation of the HPA axis, resulting in raised levels of cortisol and corticotropin-releasing hormone, both of which have been proven to rise in depression patients in studies. According to reports, patients treated with interferon- show evidence of depression due to HPA axis activation (Adu et al., 2021; Dhrisya et al., 2020). As a consequence, COVID-19 infection causes hyperinflammation, which inhibits serotonin biosynthesis and causes hyperactivation of the HPA axis, resulting in MDD. Additionally, some studies demonstrate that social isolation produces dysregulation of cytokines and increases pro-inflammatory factors; other studies have shown that quarantine can alter the regulation of emotions in vulnerable people, and that both aspects have an impact on MDD (Raony et al., 2020; Steardo and Verkhratsky, 2020). As a result of the COVID – 19 pandemic, quarantine measures have a negative impact on depression due to separation from others and dysregulation of cytokines as a result of this separation.

Finally, dysregulation in cytokine levels, whether as a result of COVID-19 infection or as a result of COVID-19 pandemy, can have a direct impact on depression-related disorders such as MDD.

2.5. Suicidal ideation

According to the last information, every 40 s, one person dies by suicide, and the second reason for death among young people is suicide (Møller et al., 2021). The most important psychosocial factors that influence the suicide rate when a virus pandemic strikes are emotional factors such as fear of being infected or long-term social isolation. The second culprit is the immune system’s response, which leads to hyper-inflammation (Dhrisya et al., 2020; Leaune et al., 2020). According to previous studies, emerging pandemics accelerate the number of suicides. There was an increase in the number of suicides reported during the
2.6. Psychosis

Psychosis is sometimes defined as delusions or hallucinations (Dave et al., 2020). SARS-CoV infection has been linked to psychotic disorders in the past, and during the 1918 influenza outbreak, research revealed 100 patients with neuropsychology symptoms related to infection, 48 of them had psychosis (Smith et al., 2020a). Furthermore, multiple studies have found a link between COVID-19 and psychotic disorder (Brown et al., 2020; Correa-Palacio et al., 2020; Ferrando et al., 2020a, 2020b; Huaracaya-Victoria et al., 2020b; Rentero et al., 2020; Watson et al., 2021). COVID-19 has been linked to psychotic disorders in a variety of ways, including hyperinflammation, neurotoxicity, and psychological stressors (Smith et al., 2020a; Watson et al., 2021). Neuronal filament light (NEFL) is one of three neuronalfilament family members which can be used as a biomarker to assess neuro-axonal damage. The NEFL mRNA level was found to be significantly higher in first-episode schizophrenia patients compared to healthy individuals in the Zhang et al. study (Tang et al., 2021). Interestingly, in Ameres et al. study, it was shown that COVID-19 is associated with increased serum NEFL levels, indicating the possible correlation between COVID-19 and schizophrenia (Ameres et al., 2020). Several investigations found a link between COVID-19 infection and the immune system or inflammation, and the majority of authors concluded that the etiology of COVID-19-related psychosis is most likely caused by excessive inflammation and persistent immune system activation (García, 2020; Santos et al., 2021; Shi et al., 2020; Tay et al., 2020; Thomas, 2021; Zhang et al., 2020). Lim et al. (2020) described a 55-year-old white woman in the UK with no history of mental illness who was admitted to the hospital with COVID-19 symptoms and returned two days later with ongoing paranoid delusions and auditory hallucinations. TNF- was increased, but IL-6 was not, implying that a high TNF level correlates with psychosis (Thomas, 2021). Another study by Ferrando et al. found that all three cases of COVID-19 patients had an elevation in C-Reactive Protein (CRP; a latent marker of immunological activation), which was linked to psychosis. (Ferrando et al., 2020a). As a result, hyperinflammation may have a role in psychosis as well as the other psychiatric conditions discussed before.

As previously stated, another mechanism of psychosis linked to COVID-19 is the virus’s entry into the CNS. The virus can enter intranasally through the olfactory bulb, move to the anterior cingulate, and then disseminate in the brain via the basal forebrain. The virus can also be transmitted via the BBB via the hematogenous route, which involves two mechanisms: the first is through vascular endothelial cells, and the second is by leukocyte infection and transmission across the BBB (Beach et al., 2020; Santos et al., 2021; Szczęsniak et al., 2020). Post-mortem studies showed that the COVID-19 could enter the brain (Reza-Zaldivar et al., 2020). Also, it is reported that RNA of COVID was isolated from the CNS of patients (Smith et al., 2020b). The brainstem seems to be the major target for the SARS-CoV. There are two crucial nuclei in the brainstem: the solitary tract’s nucleus and the nucleus ambiguus (Szczęsniak et al., 2021). COVID-19 has neuroinvasive properties as autoimmune or viral replication and probably belongs to a class of CNS opportunistic pathogens (Ferrando et al., 2020a).

Stress and anxiety caused by a high rate of viral infection or an increase in the number of people dying are other factors that influence psychosis during a pandemic. This issue has been the subject of certain reports. A 38-year-old woman with no previous psychiatric history and negative COVID testing was the subject of a case report in Peru. Due to the psychosocial stress connected with COVID-19, she developed an acute psychotic disorder and was treated with quetiapine 500 mg/day and clonazepam 1 mg/day (Huaracaya-Victoria et al., 2020a). Another study described four cases in which the anxiety of COVID-19 caused delusions. One patient had a family history of psychosis, and two patients had adjustment disorder and brief psychotic disorder, respectively (Valdés-Florido et al., 2020). So, virus-induced stress during a pandemic can also affect mental illness, especially psychosis.

3. Conclusion

According to this fact, the coronavirus pandemic has a significant impact on mental health through several ways, like hyper inflammation, the penetrance of the virus in the CNS, and the psychosocial stress associated with COVID-19. It is needed that management and prevention interventions be made.

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In recent years, when the world has been plagued by the deadly COVID-19 pandemic, this study is dedicated to all those who have lost their lives. The authors of this article also present this study to all physicians, nurses, and medical staff in the world who have rendered valuable services in combating this pandemic.

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