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Coronavirus Infection and Mood Disorders: Possible Mechanisms and Pathophysiology

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Abstract: Emerging evidence suggests elevated rates of mood disorders such as agitation, confusion, post-traumatic stress disorder (PTSD), depression and psychosis in the general population during the coronavirus pandemic. In this review, we discussed the etiologic factors and pathophysiology underlying mood disorders development during the COVID-19 pandemic.

Based on present evidence, the main pathophysiological mechanisms involved in the association of COVID-19 infection with mood disorders can be considered as the direct effect of coronavirus infection on the brain, and the effect of immune system response induced-inflammation on the brain. Moreover, psychological stresses including social isolation, fear of infection, fear of family members' infection, conflicting messages and instructions about public health measures and economic problems can lead to mood disorders. It seems that virus-immune system interaction-induced or stress-induced inflammation can play the most effective role in the promotion of mood disorders via structural and functional impairments in different areas of the brain, especially in limbic structure.

Due to the incidence of mood disorders in the coronavirus pandemic, it seems necessary to pay attention to preventive or therapeutic interventions to management of neuropsychiatric manifestations parallel with therapeutic interventions of other clinical symptoms.

Keyword: Covid-19; Coronavirus; Mood disorders; Inflammation; Stress

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1. Introduction

The novel coronavirus disease called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19 was emerged in China in late 2019 and declared by the World Health Organization (WHO) as the largest outbreak and a serious threat to public health in the modern world (1).

The coronavirus usually affects the upper respiratory tract and has flu-like symptoms including fever, cough, dyspnea, and other respiratory problems (2). Viral infection of the respiratory tract can have several systemic effects on central nervous system (CNS), and thus may cause a spectrum of neurologic and psychiatric disorders. Indeed, neurological and psychological problems such as confusion, agitation, fear, post-traumatic stress disorder (PTSD), anxiety and depression have been reported following this disease (3-5).

During the first wave of infection in China, Chen et al. described the epidemiological and clinical characteristics of 99 patients with the coronavirus. Among them 4% had headaches and 9% had confusion and meningitis (6). A few months later, Mao et al. retrospectively analyzed 214 patients diagnosed with Covid-19 from three different hospitals. About 4% of the study population had neurological disorders that included different manifestations of central, peripheral, or musculoskeletal, as well as psychological symptoms. Headache and confusion were the most common manifestations in COVID-19 patients and delirium, anxiety and depression were also common psychiatric symptoms (7). Moreover, some elderly patients who were hospitalized for coronavirus were reported to have disorders ranging from mild drowsiness to delirium compared to young and middle-aged patients (8). Onset or exacerbated symptoms of acute psychosis and manic disorders

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such as schizophrenia have also been reported in some cases of Covid-19 (2, 9). Psychiatric symptoms were worsened even after the use of common medications in the treatment of Covid-19 disease (10). A meta-analysis by Rogers et al. has shown the prevalence of mood disorders including post-traumatic stress disorder (32·2%), depression (14·9%), anxiety disorders (14·8%) and memory impairment (18.9%) in the post-illness stage in covid-19 patients (4).

The etiology of the psychiatric consequences of infection with coronavirus is probably multifactorial and may include the direct effects of viral infection on the brain, procoagulant state of the cerebrovascular system, the degree of brain hypoxia, the immunological responses and medical interventions (4, 11).

Moreover, some investigations highlighted onset or exacerbated mood disorders in non-infected individuals due to psychological stress or adverse lifestyle changes occurring in response to the COVID-19 pandemic (12, 13).

As mentioned above several observational studies have reported the prevalence of different mood disorders in infected patients during the coronavirus pandemic, but fewer studies have discussed the etiologic factors and pathophysiologic mechanisms underlying covid-19-related mood disorder development. In this review, we have tried to have a comprehensive look at the psychosocial factors and pathophysiologic mechanisms affecting the onset or exacerbation of mood symptoms and prevalence of mood disorders in infected and in non-infected individuals during the coronavirus pandemic.

2. Factors affecting the onset or exacerbation of mood symptoms in non-infected individuals

Emerging evidence reported high rates of pos- traumatic and psychological stress in the general population due to the COVID-19 pandemic (14, 15). Psychological stress and genetic vulnerability are key factors in the etiopathogenesis of mood disorders. Psychosocial investigations have highlighted the importance of stressful events as a risk factor for the development of mood disorders such as anxiety, depression and schizophrenia (16, 17).

One of the psychological stresses during the COVID-19 is social isolation. Implementing social distancing and quarantine policies to control or limit the spread of the coronavirus infection can have an impact on both affected and healthy populations and lead to psychological disorders. Imposed quarantine or isolation is an unpleasant experience that involves separation from friends and family, and a departure from usual everyday activities. Laboratory studies indicate that social isolation aggravates hippocampal cell injuries, neuronal apoptosis, and memory impairments in rats after traumatic brain injury (TBI) and social enrichment reverses the isolation-induced deficits of hippocampal neuronal plasticity (18, 19). Social isolation is one of the reliable animal models for anxiety and depression studies (20). Long-term social isolation stress induces behavioral disturbances, including aggression, hyperlocomotion, cognitive deficits, and anxiety-related behavior in laboratory animals (21, 22). Also, several lines of clinical evidence have shown social isolation is associated with a higher risk of mental health problems such as depression, anxiety, sleep disorders, bipolar and substance use disorders (23-25).

In addition to social isolation stress, several other psychological stressors can threaten the mental health of individuals during the Covid-19 disease pandemic, such as fear of infection to the novel severe and potentially fatal coronavirus, fear of contact with people infected with the virus especially in the medical staff and other high-risk occupations, fear of infecting other family members, concerns about lack of access to testing and medical care, conflicting messages and instructions about public health measures, economic problems and constant media coverage about the prevalence of the disease, and uncertainty about the final result (26-28) (Figure.1).

Moreover, in terms of public mental health, feelings of insecurity and/or anxiety and stress are the main psychological risks for addictions which in turn can put consumers at greater risk for mental disorders. Evidence indicated that internet, alcohol and substance use has increased dramatically during the COVID-19 Pandemic. People who have a small amount of alcohol or substance use have shown increased consumption of them, and people who had a history of alcohol or substance use have shown a higher rate of re-use (29, 30). Drug addiction increases the susceptibility to mental illnesses such as schizophrenia (31). Alcohol and substance use are associated with depressive and anxiety disorders, and the greatest risk of self-harm and suicidal behavior (32-34). Moreover, computer, cell phone, or online addiction named Internet Addiction Disorder (IAD) can lead to mental health problems like attention deficit, hyperactivity disorder, obsessive-compulsive disorder, depression, hostility, hypomania, and social anxiety disorder (35, 36). IAD was common among patients with psychiatric disorders during the COVID-19 pandemic (37).

2.1. Effect of stress on mood disorder development

Coronavirus infection-induced physical stress or psycho logical stress during this disease can be one of the main factors in the development of mood disorders during the coronavirus pandemic, both in patients involved in covid-19 disease and in noninfected peoples. Severe or extended exposure to stress causes long-term upregulation of the HPA axis. Environment-induced stress stimuli can directly affect cortico-limbic circuit activity and increase glucocor-

ticoid levels by HPA axis hyperactivity. Chronic exposure to supraphysiologic levels of glucocorticoids is associated with structural and functional brain changes and an increased prevalence of psychiatric disorders, cognitive impairment, mood alterations, and sleep disturbances (38, 39).

Also, clinical research has indicated that long-term or excessive exposure to stress overactivated inflammatory state and is associated with increased risk and severity of a variety of mood disorders. Two physiological pathways are responsible for stress translation into broad proinflammatory programs. The first pathway involves the sympathetic nervous system (SNS), and the second pathway involves the hypothalamic-pituitary-adrenal (HPA) axis (40).

The first effector pathway that regulates systemic inflammation is the SNS. This pathway allows the central nervous system to manage innate immune responses between pro-inflammatory and antiviral phenotypes. The SNS promotes pro-inflammatory cytokine production by releasing the norepinephrine into the vasculature and perivascular tissues and lymphoid organs. Norepinephrine modulates immune response gene transcription via stimulation of β-adrenergic receptors (41). On the other hand, norepinephrine by α-adrenergic signaling cascade suppresses transcription of antiviral type I IFN genes and upregulates transcription of the pro-inflammatory immune response genes such as IL-l, TNF-α, and IL-6 and leading to increases in systemic inflammatory activity that can lead to mood disorder development (42, 43).

The second effector pathway is the HPA axis. Under normal stress, activation of the HPA axis inhibits (rather than promotes) transcription of both pro-inflammatory and antiviral immune response genes by stimulating the release of glucocorticoids, mainly cortisol, from the adrenal cortex. Glucocorticoids are potent anti-inflammatory agents. mediate their inhibitory effects on immune response gene transcription through three mechanisms: 1. glucocorticoid binds to the glucocorticoid receptor (GR) and activated GR binds to gene promoter sequences and interrupt proinflammatory gene expression. Also, GR activation can promote the expression of anti-inflammatory genes, which inhibit pro-inflammatory transcription factor NF-κB and block the inflammatory cascade initiated by this transcription factor (44, 45).

However, under severe or long-term stress, a different set of events can occur, leading to HPA axis-related increases (as opposed to decreases) in inflammation. The process underlying this phenomenon is referred to as glucocorticoid resistance or glucocorticoid insensitivity. In this condition, immune cells become less sensitive to the anti-inflammatory effects of glucocorticoids to compensate for their persistent glucocorticoid secretion. In other words, glucocorticoids and proinflammatory cytokines are steadily increasing to coordinate with each other (as positive feedback) in response to long-term or severe stress (40, 46).

3. Mechanisms affecting the incidence of mood disorders in patients with coronavirus

Through a review of previous studies, it was revealed that the main pathophysiological mechanisms involved in the association of COVID-19 with mood disorders can be considered as a) the direct effect of coronavirus infection on the brain, and b) the effect of immune system response induced-inflammation on the brain. In the following, we

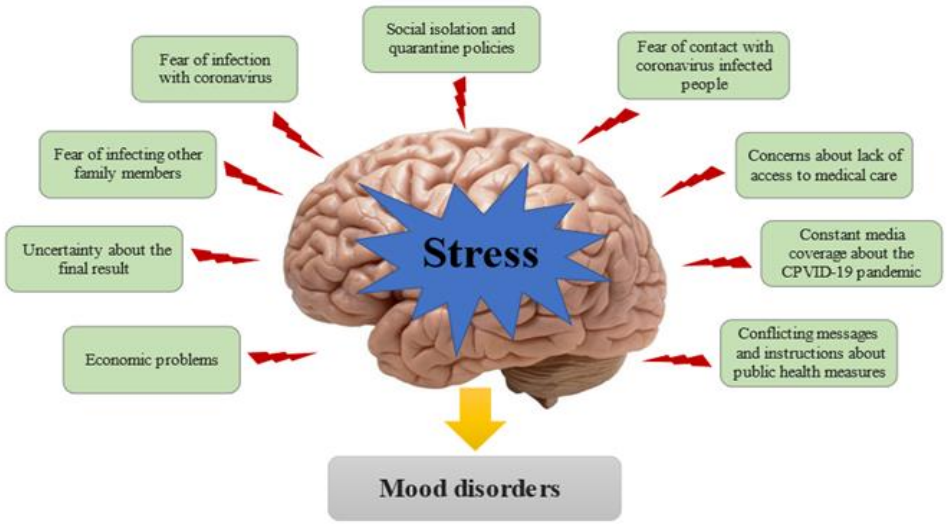

Figure 1: Psychological risk factors for development of stress- induced mood disorders during coronavirus pandemic

discuss the role of each of these factors in the development of mood disorders during the COVID-19 prevalence (figure 2).

3.1. The direct effect of coronavirus on the brain

Animal models have shown that the coronavirus can directly attack the limbic system structures, and this may explain the symptoms of psychosis in coronavirus patients (47). The limbic system including hypothalamus, amygdala and hippocampus is involved in behavioral and emotional responses and cognition (48). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) to enter target cells, and for efficient cell entry needs proteolytic processing of the spike protein by transmembrane protease serine 2 (TMPRSS2) (49). The ACE2 which is a cardiovascular and cerebral protective agent is expressed in various organs including the nervous system and smooth muscles. ACE2 is an important target for various viruses including coronavirus and influenza (50). Viruses bind to ACE2 and causing abnormally high blood pressure and an increased risk of a cerebral hemorrhage. Moreover, SARS Covid-2 via the binding to the ACE2 expressed in the capillary endothelium damages the blood-brain barrier (BBB) and easily enters the central nervous system. The risk of coronavirus attack on the central nervous system increases with age, high virus volume, weakened immune system, glucocorticoid use, a history of past viral infections, and increased hospital stay (47).

Studies on both animal and human models have shown several different neural pathways are involved in the COVID-19 disease. In rodents, after inoculation of the coronavirus, it was detected in the olfactory bulb after 4 days and in the piriform cortex after 40 days (27). The coronavirus can also propagate in the cortex, hypothalamus, thalamus, amygdala, basal ganglia, and brainstem (26). ACE2 can lead to stimulation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (51, 52). Hyperactivity of the HPA axis is one of the main factors in the development of mood disorders (53). Clinical evidence suggests that angiotensin 2 converting enzyme inhibitors (ACE2 inhibitors) or angiotensin receptor blockers had positive effects on mood disorders (54). It was shown that ACE gene expression is associated with disorders such as depression (4), and ACE inhibitors such as captopril have shown antidepressant effects (55). Also, reduction of depressive behavior symptoms has been reported in angiotensin knockout mice (4).

In addition to entering through BBB, coronavirus may also enter the nervous system directly through synaptic transmission when inhaled, without the use of ACE2 (56). In fact, the neural pathways are very important factors for entering the virus into the central nervous system. After infecting the sensory or motor nerve terminals, the virus can reach the central nervous system through retrograde or anterograde neurotransmission by dynein and kinesin motor proteins. After the invasion, the virus triggers a large cascade of neuroinflammation by activating the reactive astrogliosis process and hyperactivity of the microglia.

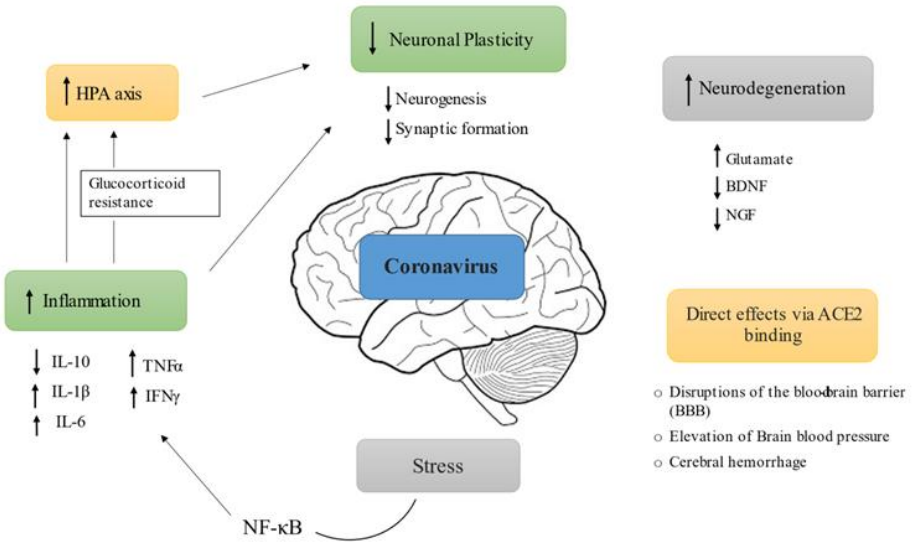

Figure 2. Mechanisms affecting the incidence of mood disorders in coronavirus pandemic. The main pathophysiological mechanisms involved in the association of coronavirus pandemic with mood disorders can be considered as the direct effect of coronavirus on the brain, and the effect of infection-induced and/or stress-induced inflammation on the brain. These mechanisms lead to neurological impairments such as neurotrophins reduction, decreased neuronal plasticity and increased neurotoxicity, followed by mood disorders.

The infection of the central nervous system with the virus results in the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1B), nitric oxide, prostaglandin E2 and oxygen and nitrogen free radicals (ROS & RNS), as well as macrophages, microglia and astrocytes disfunction. Eventually, it causes chronic neuritis and neurodegeneration (57).

Pro-inflammatory cytokines interact with almost all pathophysiologic domains involved in the development of depression, including neurotransmitter metabolism, HPA axis function, neurogenesis and synaptic plasticity (58, 59). An association between mood disorders such as depression and a decrease in the number of neurons in the hippocampus, prefrontal cortex and amygdala has been observed (60). Glial cell dysfunction also plays a vital role in the pathophysiology of mood disorders (61). These cells play critical roles in regulating synaptic communication and in releasing trophic factors that participate in the development and maintenance of synaptic networks, so abnormalities of glial function could result in impairments of structural plasticity and the overall pathophysiology of mood disorders (60, 62).

3.2. The effect of immune system response induced-inflammation on the brain

Of the potentially destructive effects of inflammation, following the activation of the immune system, is a change in mood, sleep, energy, cognition and motivation, which all are part of the symptoms of mood disorders. Evidence from several lines of research implicates immuno-inflammatory mechanisms in the brain and periphery in the etiopathogenesis of mood disorders. The main findings are an increase in the levels of proinflammatory cytokines with a decrease in neurotrophic support during mood disorders (63-65). The entry of the virus into the body organs including the respiratory system leads to the release of large amounts of pro-inflammatory cytokines such as IFNα, IFNγ, IL-1β, IL-6, IL-12, TNFα, TGFβ and also chemokines such as CCL2, CCL3, CCL5 and CXCL8 by the immune system. In this regard, can point to an elevation of pro-inflammatory cytokines such as prostaglandin E2, TNF-α, IL-1β, IL-2 and IL-6 in the serum and cerebrospinal fluid of patients with major depressive disorder and bipolar disorder (66). Cytokine overproduction cause dysfunction of various organs of the body, including the central nervous system. These cytokines have a potential role in neurogenic inflammation that one of the first manifestations of which is headache, one of the most common symptoms of COVID-19 (67-69).

Peripheral pro-inflammatory cytokines enter the neural environment by destroying the blood-brain barrier. Cytokines in the nervous system can increase the entry of calcium into neurons and cause neurodegeneration due to intensifying the secretion of neurotoxic compounds and subsequently activating glutamate receptors (70, 71). These toxic compounds including glutamate are secreted by activated microglia and astrocytes. The pro-inflammatory cytokine IL-Iβ, expressed in activated microglia and astrocytes, increases glutamate release from astrocytes and decreases glutamate reabsorption, resulting in increased neurotoxicity (72-74). Neurodegeneration in the hippocampus may occur directly through activation of the glutamate system or by reduction of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (75, 76). Recent studies have shown the coronavirus-induced pathological process can be linked to the glutamate excitotoxic mechanism. Coronavirus infection causes neuronal degeneration as an outcome of glutamate excitotoxicity (77-79). Moreover, reduction of serum BDNF level has been found in SARS-CoV-2 patients and the level of this reduction has correlated with age and severity of infection (80, 81). Basic and clinical evidence suggests that a decrease in hippocampal volume followed by various structural and neurochemical alterations in neurotrophic levels, especially BDNF reduction as well as an increase in cytokines including IL-6 and TNF-α plays a vital role in depression (70, 71). The hippocampus is rich in BDNF, which plays a key role in the growth, maturation and survival of neurons, as well as neurite formation and synaptic plasticity in the adult brain. The coronavirus by reducing BDNF disrupts neuronal survival. This decrease may be due to increased cortisol levels or decreased activity in monoaminergic neurotransmission or other harmful factors (including high glutamate secretion) (70, 71).

4. Conclusion

In this review, we discussed the factors involved in coronavirus-induced mood disorders during the COVID-19 prevalence.

Based on present evidence, it seems direct brain infection with the virus and immune system responses to the infection, and also the physical and/or psychological stress can increase the risk of mood disorders. Considering mechanisms involved in the development of mood disorders, it seems that inflammatory factors can play the most effective role in the promotion of mood disorders via structural and functional impairments in different areas of the brain especially, in the limbic system.

It is believed that during the treatment of respiratory, cardiac and renal clinical symptoms in Covid-19 patients, clinicians must be aware of the possibility of mood disorders such as depression, anxiety, PTSD, and other neuropsychiatric syndromes in the aftermath. Therefore, it seems necessary to pay attention to therapeutic interventions to prevent or alleviate mood symptoms in parallel with therapeutic interventions for systemic clinical symptoms.

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6. Conflict of interest

The authors have no conflict of interest in this research.

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8. Author contribution

None.

9. Reference

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