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THE CORRELATION BETWEEN PSYCHIATRIC DISORDERS AND COVID-19: A NARRATIVE REVIEW

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SUMMARY

Since December 2019, the havoc caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has increased exponentially in a short period of time. As the COVID-19 pandemic is raging around the world, scientists are trying to reveal its mysteriousness. Although COVID-19 is predominantly a respiratory disease, the most common symptoms are fever, dry cough, and fatigue, but extrapulmonary manifestations are increasingly recognized. Recent studies have shown that there is a strong genetic correlation between one or more psychiatric disorders and the occurrence of SARS-CoV-2 infection. Historical epidemiological perspectives and recent neurobiological evidence link infection and psychosis. What is the relationship between COVID-19 and psychiatric disorders? In this article, we will review the correlation between COVID-19 and psychoses, the possible reasons, and the possible pathophysiological mechanisms. The purpose of this review is to provide a reference for clinicians to make correct judgment and treatment when facing patients with COVID-19 and/or psychiatric disorders.

Key words: *psychiatric disorder - COVID-19 - SARS-CoV-2 - psychiatry - neuropsychiatry*

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INTRODUCTION

COVID-19 pandemic is not only a great impact on almost all aspects of personal life and organization in the world (Cucinotta & Vanelli 2020) but also an important source of psychological stress (Taubman-Ben-Ari et al. 2020). The unpredictability and uncertainty of the COVID-19 epidemic, related blockades, physical distances, and other containment strategies, as well as the resulting economic collapse, may increase the risk of psychiatric disorders (Rajkumar 2020, Gupta et al. 2020). Recently, there have been more and more studies on the relationship between COVID-19 and psychoses (Nalleballe et al. 2020, Varatharaj et al. 2020). However, there is little information to date on a comprehensive review of the subject. In this review, we collect evidence of the associations between COVID-19 and psychoses, the possible reasons, and mechanisms. Our purpose is to remind clinicians that when facing patients suspected of COVID-19, they should consider that COVID-19 may be complicated with psychiatric disorders, to avoid misdiagnosis of COVID-19. At the same time, early diagnosis and treatment of psychoses in patients with COVID-19 can prevent further deterioration of late neuropsychiatric complications.

What is already known about this topic? - Many studies have shown that there are some associations between COVID-19 and psychiatric disorders.

What is added by this review? - COVID-19 may increase the incidence of psychiatric disorders and aggravate the severity of the original psychiatric disorders. And vice versa, patients with pre-existing psychiatric disorders are more susceptible to COVID-19 and can aggravate the severity of COVID-19. The etiology of the psychiatric consequences of the COVID-19 pandemic may be multifactorial. The possible pathophysiological mechanisms include direct viral infection, inflammatory reaction, autoimmunity, hypoxia, and hypercoagulable state.

What are the clinical implications for the future? - Long-term follow-up and prospective studies are necessary to determine the real effect of COVID-19 on psychopathology.

THE CORRELATION BETWEEN COVID-19 AND PSYCHIATRIC DISORDERS

The arrival of a pandemic may become the main trigger for the beginning or aggravation of some harmful psychological characteristics, which may lead to behavioral/mental symptoms of clinical concern, which in turn will increase individual susceptibility to COVID-19 and aggravate the severity of COVID-19. Many studies have shown that COVID-19 is closely related to psychoses recently.

COVID-19 may increase the incidence of psychiatric disorders and aggravate the severity of the original psychiatric disorders

COVID-19 is a potentially fatal disease and a major source of stress for COVID-19 patients. During the pandemic, isolation, social distance, personal income instability caused by a sharp rise in unemployment, a shortage of social life resources, limited hospital resources, and barriers to access to health care

caused by stigma, these are the main problems that emerged during the COVID-19 pandemic, all of them may lead to a negative impact on mental health (Richardson et al. 2020, Myers et al. 2020, Zhou et al. 2020), and people with mental disorders may be more vulnerable to these negative effects (Adhanom Ghebreyesus 2020, Li et al. 2020, Yao et al. 2020, Shinn & Viron 2020). An observational study showed that the number of cases of schizophrenia increased by 25% in January 2020 compared with previous years, which was attributed to the psychosocial stress and physical distance measures related to the COVID-19 outbreaks (Hu et al. 2020). The review by Brown et al. postulated that there was a correlation between the high risk of psychiatric disorders and the psychosocial stress caused by the COVID-19 pandemic. The incidence of psychoses in confirmed COVID-19 patients is between 0.9% and 4% (Brown et al. 2020). Zheng noted a high prevalence of psychiatric disorders among survivors of the COVID-19 epidemic (Zheng 2020). A research showed that patients with obsessive-compulsive disorder (OCD) quarantined during the COVID-19 outbreak had higher obsessions and compulsions symptoms than before the outbreak (Davide et al. 2020).

National quarantine regulations during outbreaks make it more difficult and impractical to regularly go to outpatient clinics for evaluation and obtain prescription psychotropic substances, which can also increase the recurrence or deterioration of their pre-existing signs and symptoms (Mao et al. 2020). Also, COVID-19 infection per se and severe side effects of antiviral treatment may also aggravate some symptoms of psychiatric patients (Russell et al. 2020, Cortegiani et al. 2020, Sato et al. 2020). Individuals who suffer from mental health issues may be more especially vulnerable to the emotional response of the COVID-19 epidemic, resulting in worsening symptoms of pre-existing psychiatric disorders and/or an increased recurrence rate, because compared with the general population, they are highly sensitive to stress, such as alcohol substance use (Sun et al. 2020), eating disorders (Castellini et al. 2020). Symptoms of anxiety and depression, as well as high-stress levels, were reported after the outbreak (Mazza et al. 2020).

Patients with pre-existing psychiatric disorders are more susceptible to COVID-19 and can aggravate the severity of COVID-19

Pre-existing psychiatric disorders may also change the individual susceptibility to COVID-19 (Holmes et al. 2020). When epidemics occur, people with psychiatric disorders are generally more vulnerable to infection (Batty et al. 2020). Emerging evidence suggests that there is a strong genetic link between at least one psychiatric diagnosis and the occurrence of infection, which provides additional support for this thought. Individuals with psychiatric disorders have a higher risk of developing COVID-19, especially the hospitalization and mortality associated with COVID-19. A variety of factors may contribute to a higher risk of SARS-CoV-2 infection and worse outcomes in people with psychiatric disorders (Nudel et al. 2019). First, psychiatric disorders may increase the risk of infections (Xiao 2020, Hamada & Fan 2020). Possible explanations include cognitive impairment, lack of risk awareness, reduction in personal protection measures (such as hand washing, social distance, or isolation), and restrictions in psychiatric wards. Secondly, people with pre-existing mental disorders may face more barriers in accessing timely medical services after being infected with COVID-19 (Muruganandam et al. 2020), because of discrimination related to psychoses in the health care environment and their knowledge, skills, and access barriers to using telemedicine. Third, the coexistence of psychiatric disorders and COVID-19 will make the treatment more challenging and maybe less effective (Asmundson & Taylor 2020). For example, people with known OCD may frequently self-monitor their temperature to check for fever, or they may try to swallow saliva several times to check for throat pain as a symptom of COVID-19. Hand-washing is an important preventive measure for COVID-19 transmission, which further aggravates the suffering of patients with known washer OCD. Finally, individuals with severe psychiatric disorders are more likely to suffer from co-existing diseases associated with a higher risk for severe COVID-19. Studies have shown that co-existing diseases (such as cancer, cardiovascular disease, obesity, type 2 diabetes) contributed to higher SARS-CoV-2 infection risk in patients with recent psychosis (Shinn & Viron 2020). Patients with both COVID-19 and recently diagnosed psychiatric disorders have an increased risk of death (Wang et al. 2020).

POSSIBLE REASONS

The etiology of the psychiatric consequences of the current COVID-19 pandemic may be multifactorial, including brain infection, direct effects of cerebrovascular disease in a hypercoagulable state, response to pandemic-related stress (such as health intervention, social isolation, or stigma) (Wasserman et al. 2020), drug use (such as corticosteroids or antiviral drugs), and vertical transmission.

Reactive response to pandemic-related stress

The social distance and other public health interventions to curb the spread of COVID-19 may have an immediate and long-term impact on people with psychosis or people at risk of psychiatric disorder (Brown et al. 2020). During the pandemic, almost every country has developed public health strategies to curb the spread of COVID-19, including quarantine of people who may be exposed to the virus and requiring a physical distance from the general population (World Health Organization 2020). The incidence of depression and anxiety in

people who implement social distance may be affected (Brooks et al. 2020). Despite telecommunications tools exist, distrust or unfamiliarity with technology may be additional pressure for people with mental disorders who use such tools. The COVID-19 pandemic has caused a considerable increase in unemployment rates, restricting individuals with psychiatric disorders from having a steady income, limiting their access to food, permanent housing, and medicine (Yancy 2020). Shortages of resources that patients rely on, such as transportation, groceries, and services from public buildings, further disrupt daily life. In addition, there are the impacts of reduced physical activity, dietary changes, and reduced sunlight exposure (Lippi et al. 2020). A study indicated that self-isolation was related to the increased C-reactive protein (CRP) level (Uchino et al. 2018). Busch et al. noted that individuals with greater stress were associated with higher inflammation levels (Busch et al. 2018). These results provide a basis for the conclusion of this study: self-isolation is a special form of inflammation. This can arise through psychosocial stressors irrespective of infection, for example, fear, isolation, bereavement, homelessness, broken relationships (divorce/separation), unemployment and financial difficulties, domestic violence, and deteriorating physical health. Given their susceptibility to social health determinants, all of these may have a particular effect on psychiatric patients (Odriozola-González et al. 2020, Wang et al. 2020, Anglin et al. 2020). Similarly, the direction of this effect is unclear, as pandemics have the potential to strengthen social inequalities, which in turn may lead to a risk of exceeding the consequences of the infection itself, further complicating the interaction between COVID-19 and psychiatric disorders.

SARS-CoV-2 infection

The effect of SARS-CoV-2 infection on the brain is associated with the excessive physiological and psychological stress of stimulating the hypothalamic-pituitary-adrenal axis, which further aggravates neuroinflammatory status. The duration and frequency of exposure to stressors impact neuroinflammation, which can be exacerbated by repeated or prolonged exposure to strong stressors (O'Callaghan & Miller 2019). Long-term stress can enhance inflammatory response by releasing several pro-inflammatory cytokines. Neuroinflammation is an important aetiological factor for many neuropsychiatric and neurocognitive diseases, including neurodegenerative disorders (Bright et al. 2019), depression (Bakunina et al. 2015), psychosis (Marques et al. 2019), autism (Bjorklund et al. 2016), drug abuse (Kohno et al. 2019), and sleep disorders (Nadjar et al. 2017). A study on neuropsychiatric consequences of SARS conducted 30-50 months after infection showed an incidence of post-traumatic stress disorder (PTSD) was 40%, depression was 36.4%, OCD was 15.6%, and with the same incidence of anxiety disorders (Troyer et al. 2020). Given this evidence, the sequelae of long-term post-SARS-CoV-2 psychiatric disorders are noteworthy. A recent study indicated the neuroinvasive nature of the virus and its possible route of transmission to the central nervous system by transmission electron microscopy of the brain tissue of a 74-year-old male patient with COVID-19 (Paniz-Mondolfi et al. 2020). It has clearly demonstrated that there are 80 to 110nm viral particles in the vesicles of the frontal lobe and endothelial cells. Besides, the blebbing of viral particles in or out of the endothelial wall indicates the viral entry or exit across the brain microvascular endothelial cells into the nervous system.

Corticosteroids and/or chloroquine and other antiviral drugs

Corticosteroids usually induce psychiatric syndrome, including depression, mania, psychosis, and delirium, which is often referred to as 'steroid psychosis' and is considered to be a representative exogenous psychosis (Kershner & Cheng 1989, Lewis & Smith 1983). However, steroid psychosis is not a specific clinical entity but consists of heterogeneous syndromes with significantly different pathophysiological mechanisms. Psychiatric symptoms may also be secondary to side effects of drugs such as interferon and oseltamivir used to treat COVID-19 (Russell et al. 2020, Cortegiani et al. 2020). A pharmacovigilance study reported obviously neuropsychiatric side effects associated with chloroquine exposure, such as amnesia, hallucinations, depression, delirium, and loss of consciousness (Sato et al. 2020). The severity of COVID-19 symptoms and higher doses of corticosteroids were significantly related to an increased risk of experiencing psychiatric symptoms. Chloroquine may affect the dopaminergic system in the brain by changing dopamine levels, which in most cases is a high dopaminergic response. There is a substantial meta-analysis of evidence that proinflammatory cytokines are elevated in patients with primary psychosis. In fact, drugs targeting specific cytokines can cause psychosis (Pillinger et al. 2019, Goldsmith et al. 2016, Miller et al. 2011, Essali et al. 2019). High-dose steroid use has also been identified as a probable risk factor for psychosis, according to a case-control study in China (Lee et al. 2004).

Encephalopathy and encephalitis

Encephalopathy in COVID-19 may be the direct viral effect of neural invasion, an immune-mediated pathology induced by the virus, an indirect immunopathology caused by blood-brain barrier dysfunction, or a combination of all three. The virus enters the central nervous system by infecting endothelial cells of the blood-brain-barrier, epithelial cells of the blood-cerebrospinal fluid barrier in the choroid plexus, or by inflammatory cells (Li et al. 2020, Toljan 2020). More importantly, the virus can reach the central nervous

system by retrograde axonal transport. Retrograde axonal transport may be carried out through olfactory, respiratory, and enteric nervous system networks. After infecting the nasal cells, the virus can directly invade the brain, possibly through the olfactory bulbs, and rapidly spread to specific brain areas such as the thalamus and brainstem, triggering inflammation and demyelination (Bohmwald et al. 2018). SARS-CoV-2 has been detected in the cerebrospinal fluid of many patients with various psychiatric symptoms (Andriuta et al. 2020, Virhammar et al. 2020), it has provided undeniable evidence that SARS-CoV-2 can invade the nervous system. Two studies reported that 20% of patients had a complication of hypoxic encephalopathy following COVID-19, and patients who died were more likely to develop hypoxic encephalopathy than those who survived (Solomon et al. 2020, Rockx et al. 2020).

Vertical transmission

Several cross-sectional studies have shown that maternal stress, health anxiety, and social behavior interaction have changed significantly (Corbett et al. 2020, Mappa et al. 2020). The current COVID-19 pandemic may affect the fetal neurodevelopment of pregnant women during the pandemic by activating the immune system, directly due to maternal immune activation during infection, and indirectly due to inflammation exposed to maternal pressure during pregnancy. Inflammation is the common mediator of these two mechanisms. Isolation and limited movement may lead to a lack of social support from friends, relatives, and partners for pregnant women. Financial hardship, remote work, potentially violence from intimate partners, fewer pre-and post-natal appointments, and changes related to breastfeeding recommendations, which are a huge source of stress for perinatal women and their babies and can have short-and long-term harmful effects on pregnant women and babies (Burki 2020, The Lancet 2020). At the same time, studies have shown that vulnerable pregnant women are also high-risk groups with higher stress due to fear of infection or transmission of SARS-CoV-2 (Brooks et al. 2020, Knight et al. 2020). SARS-CoV-2 infection potentially triggers the maternal immune system to release a series of cytokines and chemokines (such as tumor necrosis factor-alpha, [TNF-α] IL-6) and other immune changes that may be transmitted to the foetus. Besides, critically ill pregnant women caused by COVID-19 are at risk of placental hypoxia, damaging foetal oxygen supply, which may cause growth restriction and brain development stagnation. Studies have shown that maternal immune activation can lead to psychiatric disorders through multiple potential trajectories, thus making the offspring vulnerable to the environmental risks for psychosis (Khashan et al. 2008). A recent review summarises the mechanisms, including the effects associated with each trimester, the direct impacts of viruses reaching the foetus, and the effects of maternal and foetal immune activation (Yockey et al. 2020). IgG antibodies and cytokines may passively cross the placental barrier, while IgM usually does not due to its larger molecular structure, suggesting that antibodies may be produced by the infant to cope with intrauterine SARS-CoV-2 infection. One area of psychiatric research that may provide a precedent for the longitudinal effect of COVID-19 is the relationship between intrauterine events and neurodevelopment of offspring (Khashan et al. 2008, Brown 2012). Therefore, it will be important to closely monitor the outcomes of children whose mothers infected prior to, and during, pregnancy.

CLINICAL MANIFESTATIONS OF PSYCHOSIS

Psychosis is a state of serious disconnection between personal experience and reality or loss of self-boundaries. It is mainly manifested in the existence of hallucinations and delusions. Psychosis is a hallmark or defined symptom of schizophrenia spectrum and other mental disorders, and it is related to the characteristics of other mental and behavioral disorders. The systemic inflammation and neuroinflammatory changes are related to the massive increased brain pro-inflammatory molecules, glial reactivity, neurochemical landscape alternation, and pathological remodeling of neural networks. These organic changes are accompanied by environmental stress and promote the pathological disorder of neuropsychiatry.

Psychosis can be considered to be a set of symptoms, and there are a variety of manifestations in COVID-19 patients, ranging from insomnia and anxiety to psychiatric symptoms and aggressive behavior. This pattern of psychiatric symptoms is similar to those of patients infected with SARS in previous studies, ranging from mild mental problems (such as anger, anxiety, and depressive reactions) to severe psychotic problems such as hallucinations and mania (Lam et al. 2009, Cheng et al. 2004). A study shows that the most common mental symptoms of COVID-19 patients on admission are insomnia, followed by aggressive behavior, delusions, and severe anxiety (Xie et al. 2020). Besides, it is characterized by depression (Beurel et al. 2020), substance-related and addiction disorders (Alexander et al. 2020), eating disorders, schizophrenia (Brown et al. 2020), reactive psychosis, panic attacks, OCD, post-traumatic stress disorder, agoraphobia, and other psychiatric disorders.

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS

The postulated common pathophysiologic mechanisms by SARS-CoV-2 include direct viral infection, inflammatory response, autoimmunity, hypoxia, and hypercoagulable state.

SARS-CoV-2 Structure and ACE2 receptor

COVID-19 pneumonia is caused by SARS-CoV-2 (He et al. 2020), as the seventh known coronavirus that can infect humans (humans coronavirus, H-CoV). The first six coronaviruses that can cause severe diseases in humans include Middle East Respiratory Syndrome (MERS)-CoV, HCoV-HKU1, HCoV-OC43, HCoV-NL63, SARS-CoV, and HCoV-229E (Corman 2019). The SARS-CoV-2 virion is approximate with a size of 70-100 nm (Naqvi et al. 2020). Its genome encodes four main structural proteins: Spike (S), envelope (E), membrane (M), and nucleocapsid (N). Recent studies have shown that some coronaviruses do not require all four proteins to become infectious virions (Schoeman & Fielding 2019).

ACE2 receptors are recognized as the SARS-CoV-2 receptor so far, which exist in a variety of human tissues, including type I and II alveolar epithelial cells, vascular endothelial cells, heart, liver, gastrointestinal tract (Hamming et al. 2004), as well as kidneys and testicles (Fan et al. 2020). It also presents at the cellular level of the central nervous system, such as the spinal cord, cortex, hippocampus, and cerebellum (Xia & Lazartigues 2008, Buzhdygan et al. 2020). S and E proteins play a critical role in aiding SARS-CoV-2 S proteins to interact with ACE2 receptors expressed in capillary endothelium (Baig et al. 2020).

Direct infection

The first step of SARS-CoV-2 infection is the recognition of host cell surface receptors. This step is mediated by the viral S protein, which recognizes the human receptor angiotensin-converting enzyme 2 (ACE2). The protein has two functional domains: the S1 domain contains the receptor-binding domain (RBD), which binds to ACE2, while the S2 domain mediates the fusion of the virus and the host cellular membrane (Walls et al. 2020). Therefore, the organ distribution of the ACE2 receptor is an important determinant of the virus infectivity and tropism. The second determinant step of the SARS-CoV-2 infection process is the activation of the S protein. This protein processing allows the complete activity of the S2 domain and the fusion of the viral and cellular membrane. The SARS-CoV-2 enters the cell following binding to the plasmalemmal ACE2 enzyme and then endocytosis (Liu et al. 2020, Lu et al. 2020). Literature suggests the enriched presence of angiotensin-converting enzyme 2 (ACE2) in the central nervous system (CNS) endothelial cells.91 Possibly the virus infects these endothelial cells in the CNS by crossing the blood-brain barrier (Solomon et al. 2020, Deffner et al. 2020). The neuronal retrograde mode is also suggested in a few studies, in which the virus initially invades the peripheral nervous system followed by infecting the CNS (Wang et al. 2020, Paniz-Mondolfi et al. 2020), neurotropic viruses may invade neurons through virion retrograde or/and anterograde interactions with neuronal cytoskeleton proteins. After neuronal infection, the virions may be released and transneuronal spread to adjacent or pre-synaptic neurons (Butowt & Bilinska 2020).

Inflammatory reaction

A growing body of evidence suggests that psychiatric disorders of COVID-19 patients may be associated with the level of inflammatory markers. It is well known that COVID-19 can cause increased levels of serum inflammatory markers by activating an immune response (Azkur et al. 2020). Meta-analysis data confirmed that there was a significant increase in pro-inflammatory molecules in patients with post-traumatic stress disorder, including IL-6, TNF-α, and IL-1β (Lindqvist et al. 2017, Bersani et al. 2016). However, the significance of the acute inflammatory state in the occurrence and development of neuropsychiatric sequela is unclear, which stems not only from the severity of systemic inflammation and the invasion of the brain by the virus but also from the severity of stress caused by unexpected pandemics (Northoff 2002). The alterations of GABA-ergic and dopaminergic regulation in the cortico-basal ganglia-thalamocortical circuit are related to its pathogenesis (Rossi et al. 2011). Exposure to pro-inflammatory cytokines is associated with altered GABA-ergic transmission in the basal ganglia. Other pro-inflammatory mediators such as interferon-alpha are considered to be associated with a hypo-dopaminergic state in the basal ganglia, which is considered to be a potential inducing factor to psychiatric disorders. Also, the hematological high inflammatory state of COVID-19 patients increases the blood-brain barrier permeability, destroys brain cells, and becomes a promoting factor for the occurrence of psychoses. A recent report on a case of psychosis patient with COVID-19 further implicates that the hyper-inflammatory state is related to the pathogenesis of these neuropsychiatric complications of severe COVID-19 (Kajani et al. 2020). Besides, inflammation is an example of a common biological factor that contributes to various psychiatric disorders and COVID-19 pathology. It is reported that inflammation plays a role in the pathogenesis of schizophrenia (Müller 2018), depression (Beurel et al. 2020), and bipolar disorder (Benedetti et al. 2020), as well as in the systemic manifestations of SARS-CoV-2 infection (Steardo et al. 2020).

Autoimmunity

When an individual with immune function is infected with SARS-CoV-2, he may experience excessive systemic immune responses and even die of acute respiratory distress syndrome and septic shock (Li et al. 2020). This mechanism is called immunopathogenicity, in which the virus stimulates immunity and causes the immune system to attack itself (Guo & Thomas 2017). The excessive activation of the immune system caused by SARS-CoV-2 infection leads to

massive accumulation and exudation of inflammatory substances, which is known as 'cytokine storm'. Cytokine storm may cause a sharp increase of monocytes, interferons, interleukins, macrophage inflammatory proteins, and tumor necrosis factors, leading to hyper-inflammation. This systemic inflammation causes severe encephalopathy, which can lead to symptoms of psychiatric disorders. A high level of IL-1β has been observed in COVID-19 patients, and other immune mediators including IL-2, IL-6, IL-7, IL-10 (Wan et al. 2020), and granulocyte colony-stimulating factor (G-SCF), which have strong pro-inflammatory effects and can cause neuroinflammation and brain dysfunction (Poyiadji et al. 2020).

Hypoxia

COVID-19 patients often have hypoxemia caused by respiratory dysfunction (Wang et al. 2020, Cascella et al. 2020), among which severe patients are characterized by acute respiratory distress syndrome (Murthy et al. 2020). When the bodily oxygen content changes, the brain is the first organ to be affected (Casas et al. 2017), resulting in a series of pathophysiological changes. Hypoxia can dilate intracranial blood vessels, increase intracranial blood flow, cerebral capillary pressure, tissue fluid production, brain free radicals, membrane lipid peroxidation, and endogenous inhibitors, which may affect cell energy metabolism (Mikhail Kellawan et al. 2017, Numagami et al. 1997). The increased lactic acid and oxygen free radicals and lipid peroxides produced by anaerobic glycolysis in the brain, and the weakened antioxidant system lead to blood-brain barrier dysfunction (Rosenkrantz et al. 1996). Metabolic acidosis due to hypoxia increases cerebral vasospasm and permeability, resulting in interstitial brain edema and intracranial hypertension (Boedtkjer 2018), which can lead to a series of injuries, culminating in neuronal and astroglial necrosis, apoptosis, and neurocognitive deficits (Mallet & Ryou 2017).

Hypercoagulable state

Clinical studies showed that the elevated D-dimer (Tang et al. 2020), the prolonged prothrombin time with unchanged activated partial thromboplastin time (APTT), and increased fibrinogen are commonly observed in patients with COVID-19, and the blood was in a state of hypercoagulability. One possible explanation for the increased blood coagulability is that a decreased blood oxygen activates increased the levels of inflammatory cytokines, catecholamine, plasma tissue factors (Kammerer et al. 2020), and platelet aggregation, which change capillary blood flow because of increased sympathetic activity and broader micro-endothelial damage, leading to increased blood coagulation (Toraldo et al. 2015), and capillary microthrombosis (Suresh et al. 2019), which may cause ischemic damages of small vessels in the brain, leading to psychoses.

PROSPECTS FOR THE FUTURE

In the long term, as symptoms and potential effects of COVID-19 continue to manifest, patients may be left with long-term neurological and/or psychiatric disorders on a global scale (Sinanovic et al. 2020, Roy et al. 2020). The role of intrauterine infection in the neurodevelopment of offspring born during this pandemic may not become apparent for many years for both infected and non-infected mothers. Notably, knowledge of the long-term psychiatric effects of COVID-19 on surviving patients is almost absent. The psychiatric sequelae of COVID-19 represent a serious clinical challenge, which has to be considered in complex screening, treatment, and follow-up in the future. It is necessary to conduct a long-term follow-up and a prospective study on the direct biological impact of COVID-19 on psychoses, in order to more accurately describe the incidence of psychoses related to SARS-CoV-2 during and after infection, as well as the real effect and potential pathogenesis of SARS-CoV-2 on psychopathology.

LIMITATIONS

This review has several limitations. First, most of the current papers on clinical features were designed retrospectively, which may introduce potential biases. Second, the symptoms associated with psychoses came from limited sample size observations and case studies, some of which were not classical psychiatric manifestations, and the psychiatric participation may contribute partially to these symptoms, and an overall analysis may exaggerate its role in COVID-19. Third, many involved studies have not yet been published, which may affect the results. The potential mechanism underlying psychiatric disorders in COVID-19 will be updated along with new evidence.

CONCLUSIONS

The COVID-19 pandemic poses a long-lasting challenge, which not only impacts the cardiopulmonary system but links systemic infection to psychiatric disorders. When doctors find the symptoms of psychoses in COVID-19 patients, they should always consider differential diagnosis to avoid delay or misdiagnosis. Long-term follow-up is necessary to determine the future incidence of psychiatric disorders after SARS-COV-2 infection, and prospective studies should be conducted to find out the real impact of COVID-19 on psychopathology, and finally overcome the epidemic of COVID-19.

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Contribution of individual authors:

Yanfei He designed the study, reviewed literature, and drafted the manuscript.

Ran Yu advised on the review and reviewed the final manuscript.

Junlin Ren retrieved and summarized the literature.

All authors read and approved the final manuscript.

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