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Review Article

Psychoneuroimmunology Aspects of COVID-19 Pandemic

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Abstract

Background : In December 2019 the world was struck by an outbreak of a disease in China which is now referred to as Coronavirus disease (COVID-19). COVID-19 disease is a viral infection caused by SARS-CoV-2. This disease has spread very quickly throughout the world, causing significant social and economic impacts. Now this incident is called a pandemic. There are many controversial theories up till now, especially about psychoneuroimmunology aspects. Symptoms caused by this disease vary greatly from the main attack of the respiratory system to neuro immunity system. Immune response is the key factor to invasion of this virus into the human body.
Objectives : The aim of this paper is providing comprehensive understanding regarding psychoneuroimmunology aspects of COVID-19 infection in those variable symptoms.
Discussion : Neurological symptoms might start from anosmia, loss of taste (ageusia), delirium, encephalitis, Guillain-Barre syndrome, and stroke. Behavior might be affected with specific symptom such as depression and psychosis. Neuropsychiatric sequelae had been found in past viral pandemics.
Conclusion : Psychoneuroimmunology aspects will determine the variability of symptoms of each patient. Comprehensive understanding of psychoneuroimmunology perspective will aid in promoting post-pandemic public mental health in order to handle COVID-19 properly and minimize socio-economic impacts.

Keywords : COVID-19; psychoneuroimmunology; immune responses; anosmia; encephalitis

INTRODUCTION

In December 2019, a mysterious case of pneumonia was reported in Wuhan, Hubei Province. The first case was linked to the fish market in December 2019. There were five patients treated with Acute Respiratory Distress Syndrome (ARDS). The number of cases increased rapidly from time to time. It had spread in various provinces in China, Thailand, Japan and South Korea in less than one month. Several samples of the research confirmed the etiology of the disease was a new coronavirus.[1]

This new coronavirus is also called 2019-nCoV acute respiratory disease (COVID-19). World Health Organization (WHO) declared this COVID-19 disease as pandemic on 11 March 2020.[2] Based on WHO data per 23 June 2020 the number of positive confirmed cases globally was 9,186,020. America had the highest position of 2,355,680 followed by Brazil with 1,111,348.[3]

The first COVID-19 in Indonesia was reported in March 2, 2020. There were two cases at that time. On 23 June, 2020, there were 47,896 positive cases in Indonesia. The total death cases were 2,535 persons with 6.0% of CFR (Case Fatality Rate). Based on these data, DKI Jakarta occupied the first position of 10,098 cases.[4]

COVID-19 infection had various clinical manifestations. Typical cases showed high fever, dry cough, shortness of breath, myalgia, headache, sore throat, confusion, diarrhea, nausea/vomiting, chest pain, nasal congestion, conjunctival congestion, sputum production, fatigue (malaise), hemoptysis, and chills.[5] Some patients reported neurological symptoms such asanosmia and/or ageusia, neuromuscular dysfunction, mood changes, encephalitis, meningitis, and psychosis. Those symptoms might occur in acute viral infection or few weeks/months afterwards.[6]

Some mental problems might arise. Phobia of being infected by the COVID-19, alcohol abuse, depression, anxiety, insomnia, and suicide were found. Phobia happens when reading the COVID-19 news. These conditions will disturb daily activities. Early prevention of COVID-19 phobia is critical to prevent further deterioration.[7,8]

In a retrospective study of 214 patients in Wuhan, China, it was revealed that 36% of 88 patients COVID-19 with severe infection had neurologic clinical presentations. The symptoms were headache, dizziness, loss of smell (anosmia), muscle pain, loss of taste (ageusia), weakness, cerebrovascular complications (stroke), encephalopathy, and impaired consciousness more than 24 hours. The blood test showed decreased lymphocyte count and elevated plasma COVID-19-reactive protein (CRP).[9] The same condition was found in Italy. Patients suffered from severe COVID-19 infection and had comorbidities such as hypertension, diabetes, and heart disease are at high risk of developing cerebrovascular complication such as stroke.[10]

Innate immune response is responsible in COVID-19 pathogenesis.[11] SARS-CoV2 has almost 80% RNA sequence homology with SARS-CoV, and 50% with MERS-CoV. Therefore, SARSCoV2 might use the similar immune invasion strategies. ACE2 is abundantly expressed in lung. However, it is expressed on monocyte and macrophages. It is a possible entry mechanism of SARSCoV2 into immune cells.[12]

The clinical presentation of COVID-19 infection was very variable among patients. Not every patient had neuropsychological symptoms. This paper is aimed to provide comprehensive understanding regarding psychoneuroimmunology background of COVID-19 infection in those variable symptoms.

Pathophysiology and pathogenesis of neurological symptoms in COVID-19

Neurological symptoms were usually found in elderly and patients with severe infection of COVID-19 (acute respiratory distress syndrome). [13] There were 3 groups of neurological symptoms, i.e. central nervous system (CNS), peripheral nervous system (PNS), and musculoskeletal symptoms. Central nervous system symptoms were headache, encephalopathy, dizziness, impaired consciousness, acute cerebrovascular disease (stroke), ataxia, and seizure. Peripheral nervous system manifestations were anosmia (olfactory dysfunction to loss of smell), ageusia (taste dysfunction to loss of taste), vision impairment, neuralgia, Guillain–Barre syndrome, and nerve pain. Meanwhile, musculoskeletal involvement had no specific symptoms. [9,14]

Pathophysiology of the acute neurological symptoms might be due to disseminated intravascular coagulation (related to strokes), cytokine storm (related to encephalopathy), intense inflammation and hypoxia (related to delirium).[10] Elevated of cytokine was exuberant in COVID-19 patients with severe infection. Elderly patients might be more vulnerable to delirium and post-infectious neurocognitive complications such as dementia.[15]

Peripheral nervous system symptoms

Anosmia and ageusia might be the earliest symptoms in some COVID-19 cases. Olfactory epithelial cells expressed the angiotensin-converting enzyme 2 (ACE2) receptor. SARS CoV-2 viruses infiltrated cranial nerves such as vagus nerve. Vagus nerve was involved in transduction and chemosensory processing. This might be related to anosmia and ageusia pathophysiology.[6]

Anosmia/hyposmia or ageusi/hypogeusia in acute phase might happen due to viral damage to the olfactory epithelium. Olfactory nerve and bulb could be affected and penetrated by the virus. Virus entered the

brain via the nose at the olfactory epithelium. Virus spread in transneuronal way to connected areas of the brain. Based on study of 3,191 patients, 15.3% of them (488 patients) had anosmia or ageusia in the early stage of COVID-19. The distribution was 52% for anosmia and ageusia, 20.3% was ageusia only and 27.7% was anosmia only.[5]

About 40% of adult anosmia is caused by viral infection, especially due to common cold and upper respiratory tract infection. There are more than 200 different viruses as the cause of upper respiratory tract infection. Coronaviruses account for 10–15 cases of them. Therefore, it is normal if COVID-19 caused anosmia in some infected patients.16 The American Academy of OtolaryngologyHead and Neck Surgery and the British Association of Otorhinolaryngology had recommended anosmia and ageusia to be the list of primary screening symptoms for COVID-19.[17] However, anosmia might happen acute, transient after days to week, or irreversible/sequelae.[18]

From twelve cases Guillain–Barre syndrome (GBS) in COVID-19 patients, some of them needed mechanical ventilation. The onset of viral infection to GBS symptoms was approximately ten days. The symptoms were paresthesia and progressive flaccid quadriparesis. Cerebrospinal fluid analysis revealed albumin–cytologic dissociation. The most common GBS in COVID-19 patients was Acute Inflammatory Demyelinating Polyneuropathy subtype.[14]

Central nervous system symptoms

One important finding to distinguish between encephalopathy due to COVID-19 infection or other central nervous system infection is the finding of SARS-CoV-2 RNA in cerebrospinal fluid (CSF) of a COVID-19 patient with acute neurologic symptoms including seizures.[19] Sometimes SARS-CoV-2 RNA was not found in the CSF although the clinical presentation showed obvious meningitis and/or encephalitis in COVID-19 patients with severe infection condition. This might be due to transient or low viral load in the CNS or false negative.[20,21]

American Stroke Association (AHA/ASA) Stroke Council Leadership studied stroke mechanisms in 254 COVID-19 patients. The study revealed that stroke mechanism in COVID-19 patients could include the release of pro-inflammatory cytokines. This mechanism caused plaque rupture through local inflammation, cardio embolism, or coagulation factors activation.[22] There are two mechanisms by which SARS-CoV-2 penetrates the central nervous system (CNS), i.e. vascular by damaging capillary endothelium and neuronal through the cribriform plate and olfactory bulb.[14,23]

The target of SARS-CoV-2 RNA is ACE2 receptor. ACE 2 receptor protein is expressed in the alveolar epithelial cells, small intestinal epithelial cells, the arterial and venous endothelial cells, also arterial smooth muscle cells in all organs, including glial cells and neuron of the brain. The central nervous system may also be affected through the blood vessel-rich meninges after the bloodbrain barrier is damaged.[23,24]

SARS-CoV-2 virus entered lung alveoli in lung infection. The virus use ACE2 receptor. ACE2 is also expressed vascular endothelia. Through vascular, glial cells, and neuron of the brain, virus attacked brainstem nuclei (solitary tract nucleus, nucleus ambiguous). Respiration rhythm and control could be damaged. At the end, it caused respiratory failure in COVID-19 patients.1[0,14] In long period, COVID-19 infection might cause immune mediated neurotoxic effects of central nervous system.[10]

COVID-19 infected patients with comorbid vascular disease risk factors might have higher risk of stroke. Complications could be hypotension, shock, arrhythmia, heart failure and disseminated intravascular coagulation (DIC). Those complications will increase predisposition to stroke.[14]

Psychological distress and psychoneuroimmunology background of COVID-19 pandemic

The COVID-19 pandemic is a significant source of psychological distress globally. Transient neuropsychiatric symptoms like delirium and psychosis might happen due to acute adverse reaction of corticosteroid treatment. It is usually diminished after corticosteroid was stopped.[6]

Medical staff, patients, family, children, the elderly, and the population were affected psychologically. Some psychological impacts were anxiety and too much disturbing thinking. Other symptoms are insomnia, panic, and phobia related to COVID-19. Mental problems were rarely involved in every infectious disease symptom. However, the COVID-19 has a huge effect to the mental health. The COVID-19 infection could harm the brain and mental health for society.[25,26]

Somatic symptoms in COVID-19 patients revealed that there was psychoneuroimmunology (PNI) background of COVID-19. Pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6 from the respiratory tract due to COVID-19, are usually found in higher level in major depressive disorder and functional somatic syndromes. COVID-19, depression and functional somatic syndrome have the same PNI background. Patients with previous psychiatric symptoms before COVID-19 infection tends to have new psychiatric disorders.[24]

Immune responses
Innate Immune Response

Innate immune response inhibits virus replication, increases virus clearance, enhances tissue repair, and induces a prolonged adaptive immune response against the viruses. Inflammatory responses at first are induces by innate immune response. This response recognizes the virus. Virus is detected through pattern recognition receptors (PRRs) to recognize pathogen associated molecular patterns (PAMPs).[12,27]

Interferon (IFN) type I responses and induction of effective adaptive immune response have critical roles in the next step. ACE2 is mostly expressed in type 2 alveolar cells. If ACE2 is minimally expressed in the target immune cells, other receptors may have roles.[12,28]

When aerosolized uptake of SARS-CoV-2 binds to ACE2 receptor, target cells are infected. Virus decreases antiviral interferon responses. There will be uncontrolled viral infection if the immune response is low. Cytokine storm takes place. Th1/Th17 will be activated and B cells produce antibodies.[28]

Adaptive Immune Response
Immune response of T cells

Th1 plays a dominant role in adaptive immunity to viral infections.[27] T cells, CD4+ T cells, and CD8+ T cells have critical antiviral role to balance immunity reaction towards inflammation. CD4+ T cells promote specific antibodies production by activating T dependent B cells. CD8+ T cells kill viral infected cells. CD8+ T cells are approximately 80% of total infiltrative inflammatory cells in the pulmonary interstitium in COVID-19 patients. These cells are important in combating corona viruses in infected cells.[28]

Humoral immune responses
B cells are memory cells. They secrete antibody. Humoral immunity is critical in controlling the persistent phase of coronavirus infection. The antibody response is a dynamic process. It is a complex mixture of monoclonal antibodies. The targets are different antigenic domains on the envelope glycoprotein of the virus. Meanwhile, complement system has a critical role in providing a way for the immune system to detect and manage foreign antigen.[28]

Different clinical stages of COVID-19 infection
Mason divided clinical stages of COVID-19 infection into three phases as following:[27]

Stage #1: Asymptomatic state (Initial 1-2 days of infection
SARS-CoV-2 binds to epithelial cells in the nasal cavity. The viruses start to replicate with ACE2 as the main receptor. There is limited innate immune response. Virus could be detected by nasal swabs. The patients are infectious at this moment. The RT-PCR value can be used to predict the viral load, the subsequent infectivity and clinical course.[27]

Stage #2: Upper airway and conducting airway response (Next few days)
The virus migrates down the respiratory tract. Innate immune response is further triggered. Nasal swabs or sputum will show positive result. Patients are symptomatic at this time. Approximately 80% of patients will have mild symptoms. They can be treated at home with symptomatic medicine.[27]

Stage #3 Hypoxia, ground glass infiltrates, and progression to Acute Respiratory Distress Syndrome (ARDS) (severe stage)
However, approximately 20% patients will fall into this stage. They will have pulmonary infiltrates. The virus reaches the gas exchange units and infects alveolar type II cells. The pathologic examination usually shows diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. Patients will have Acute Respiratory Distress Syndrome (ARDS).[27]

CONCLUSIONS

Psychoneuroimmunology perspective are essential in tackling this rapidly developing public health crisis in COVID-19 pandemic. SARS-CoV-2 viruses can invade central nervous system via vascular and neuronal. This virus can damage capillary endothelium, attack cribriform plate and olfactory bulb. Nervusvagus (vagus nerve), nucleus ambiguus, and nucleus solitarius might be affected. Therefore, there are anosmia, ageusia, and respiratory failure in COVID-19 patients. Innate and adaptive immune responses are crucial in defense against virus and antibody production. When the viral infection is uncontrolled, cytokine storm will take place. Mental health problem shouldn't be forgotten. Insomnia, anxiety, phobia, and suicide could happen. Psychiatric patients might develop new psychiatric disorders during the COVID-19 pandemic. Understanding psychoneuroimmunology aspects will be useful in decreasing mental health problems during the COVID-19 pandemic.

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