Neurological Aspects of Long COVID-19

by Ilsa Hunaifi

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1. INTRODUCTION

Since it first appeared as pneumonia caused by Coronavirus in December 2019, Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2) has become a pandemic. In January 2020 there are significant clinical evidence that confirm human-to-human transmission. High infectivity, upper respiratory tract (and contact) transmission, relatively long incubation period, and global travel pattern are essential elements in turning this virus into a pandemic. In February 2021, there are at least more than a hundred million people in the world who have been infected by the virus, and have been molecularly tested. More than two million deaths have been correlated with this disease [1]. Long COVID or post-acute COVID (persistent symptoms more than three weeks) is a clinical progression which is more complex than previously reported in Wuhan, China. Long COVID causes longer recovery period in COVID symptoms, even in patients with mild severity [2,3].

2. METHODOLOGY

We performed a PubMed electronic data bases search from December 2019 to April 2021 using several keywords, such as "COVID-19", "Long COVID-19", "post COVID-19" and "neurological symptoms". Multiple combinations of these terms were searched. Other useful sources in the reference lists of the selected articles were also searched as an addition. A total of 397 articles were obtained. Articles not written in English were excluded. After excluding viewpoints, and opinions and screening the title andc abstracts, 15 articles were considered eligible for our literature review.

3. RESULT

The articles included in this review consisted of one meta-analysis, one qualitative study, seven literature reviews, one multicenter study, two case reports, one observational study, one exploratory study, and one integrative classification. These studies are collected from all over the world: United Kingdom (UK), Italy, France, Mexico, Australia, Egypt, Austria, United State of America (USA), Ireland, China, and Japan. The meta-analysis that we reviewed here consisted of 48,045 samples

4. DISCUSSION

a. Definition

Long COVID or "Post-acute COVID-19", "Post COVID-19 manifestations", "Long-term COVID-19 effects", or "Post COVID-19 syndrome", is a set of signs, symptoms, or clinical parameter which linger for more than two weeks after the onset of COVID-19[4]. The term "Neuro-COVID" is used in reference to the neurological and psychiatric manifestations of COVID-19. These neurological manifestations may also persist after recovery.

b. Epidemiology and Etiology

Long COVID is frequently reported in recovered COVID patients with history of more severe and critical symptoms. Long COVID is also reported in individuals with mild infections who did not need hospital admission. Gender, ethnicity, age, viral dose, disease progression, or underlying medical condition has not yet been correlated with increased Long COVID risk. Some research found more cases of Long COVID in women [3].

In Wuhan, China, there are high incidences of neurological symptoms. Around 24.8% has Central Nervous System (CNS) symptoms, 8.9% has Peripheral Nervous System (PNS)

symptoms, and 10.7% has musculoskeletal symptoms [5]. The etiology of these neurological symptoms is complex and multifactorial, which further correlates with cerebrovascular disease (including hypercoagulation), infection, physiological compensation, adverse effects of medication, and social aspects of COVID-19 [4].

c. Pathophysiology

In patients diagnosed with viral encephalitis, gene sequencing was performed and the presence of SARS-CoV-2 in cerebrospinal fluid (CSF) was found. Some hypotheses on how this virus can enter the central nervous system are: hematogenous dissemination, neuronal retrograde transport, and entry of the virus through the nasal cavity and the cribriform plate that supports the olfactory bulb. Viruses can disseminate throughout the body via the bloodstream and damage endothelial cells by interfering with the function of Angiotensin Converting Enzyme 2 (ACE2) [6]. This virus attacks ACE2 receptors, and these receptors are found in many neural tissues [7].

SARS-CoV-2 targets the CNS through several mechanism:

1. Direct infection

Neurotropism or the ability for a virus to infect the neural system of SARS-CoV-2 is related to its affinity for the ACE2 receptor in the endothelial cells. The receptor is found in the brain and is expressed in glial cells and neurons, therefore the virus has the possibility of infecting these cells. Several studies have contrasting results regarding SARS-CoV-2 invasion in the CNS. One study did not find any presence of the virus in the brain [8], while others found viral particles in the cerebrospinal fluid and in the endothelial cells of the frontal lobe tissue [9,10]. Corona viruses may be able to enter the CNS through several hematogenous mechanisms, such as being carried by infected leukocytes which cross the Blood-Brain Barrier (BBB) and/or by directly infecting the brain vascular endothelial cells. SARS-CoV-2, however, does not implement these types of route since it was not detected in non-neuronal cells of the brain in early stage of infection [10].

Other proposed mechanism of infection is via olfactory nerves or the enteric nervous system. Olfactory nerves, however, does not express ACE2. This suggests an ACE2-independent pathway. Neuropilin-1 (NRP1) is a transmembrane receptor found in abundance on respiratory and olfactory epithelium. It is also found in the olfactory regions of the CNS. This receptor is thought to enhance the entry of SARS-CoV-2 into the brain, therefore suggesting an alternative entry route of the virus via the olfactory nerves [11].

2. Blood circulation

Other possible pathway is through the circulatory system. As the Blood Brain Barrier protects the CNS from most of the large circulating molecules, SARS-CoV-2 has to enter the CNS using intermediate cells. These cells are the endothelium and leukocytes. ACE2 is highly expressed in the endothelial cells comprising the BBB. Therefore direct damage of the endothelial cells by the virus might enable them to enter the CNS. Some coronavirus are able to infect leukocytes. As the leukocytes circulate through the BBB, SARS-CoV-2 use these cells as vectors to spread [12].

3. Neuronal pathway

SARS-CoV-2 can enter the CNS through the vagal nerve in the lungs or by enteric nerve in gastrointestinal infection. The transport of neurotropic virus to the CNS is facilitated by the motor proteins Kinesins and Dynein [13].

4. Immune mediated injury

CNS can be damaged by Cytokine Storm Syndrome (CSS) caused by SARS-CoV-2. CSS is composed mainly by Interleukin-6. Neurotropic virus can activate glial cells, leading to the production of IL-6, IL-2, and IL-5. This causes chronic inflammation of the CNS. SARS-CoV-2 can also activate CD4+, therefore causing more production of the IL-6 by macrophages [13].

Lack of ACE2 receptors causes endothelial dysfunction and can lead to neurovascular endothelitis in the brain and other organs. Hyperinflammation and endothelitis can cause

disruption of the blood brain barrier, thus allowing the entry of immune cells into the brain and causing continuous inflammation. Continuous inflammation causes hypercoagulation condition [7]. This hypercoagulated state is characterized by an increase in procoagulant factors, including serum fibrinogen, platelet, IL-6, and D-dimer. The inflammatory state also increases the levels of C-Reactive Protein (CRP), IL-7 and other inflammatory markers that make atherosclerotic plaque rupture more easily. Both of these conditions lead to an increased risk of ischemic stroke in COVID-19 patients. In COVID-19, thrombocytopenia, increased levels of D-dimers, and prolonged prothrombin time can also cause bleeding. Downregulation of ACE2 can cause disruption of the renin angiotensin system. This causes vasoconstriction and an increase in blood pressure which can lead to arterial rupture and bleeding [14].

The headache found in COVID-19 cases is thought to be caused by SARS-CoV-2 invasion of the trigeminal nerve endings in the nasal cavity. Another hypothesis is trigemino-vascular activation due to involvement of vascular endothelial cells rich in ACE2 receptors. Another possible mechanism is the release of pro-inflammatory mediators and cytokines during the infection can stimulate the trigeminal nerve endings in the perivascular area, causing headache [14].

d. Classification of Long COVID symptoms

Based on the classification made by Fernandez-de-Las Penas *et al*, long COVID symptoms are categorized into:

a. potentially infection-related symptoms, ranging from four to five weeks after the onset of infection
b. acute post-COVID symptoms which happen during the fifth to twelfth week after the onset of infection
c. long post-COVID symptoms, which happen from week 12 to week 24
d. persistent post COVID symptoms, which last more than 24 weeks [15].

e. Clinical Appearance

The most common neurological symptoms are headache, loss of attention, dementia, depression, anxiety, ageusia, anosmia, memory loss, and hearing loss. In addition, SARS-CoV-2 is also thought to cause myalgic encephalomyelitis / chronic fatigue syndrome (ME / CFS), a multisystem disease that can cause neurological symptoms such as sleep disturbances and decreased cognitive function. Other symptoms that might appear are brain fog and neuropathy [4].

Headache reported in COVID-19 is usually tension-type with moderate to severe severity. The pain is bilateral and gets worse when bending over. Pain is most felt in the temporoparietal region. Intracranial bleeding is found in 0.5% of COVID-19 patients [6].

About 40% - 88% of severe COVID-19 patients have neurological symptoms, along with symptoms of neurodegeneration, neuroinflammation, and demyelination. However, it cannot be concluded that all neurological symptoms are a consequence of virus entry into the CNS. The sequelae of COVID-19 are still not widely known but basal ganglia dysfunction as a result of neuroinflammation of the CNS has been widely seen in COVID-19 patients [6].

In Hong Kong, prolonged muscle weakness and other myopathy were found in patients who had recovered from COVID-19. It was also found that the longest lasting symptoms were neurological symptoms. This is similar to the SARS epidemic which found CNS symptoms and chronic fatigue for four years after the first infection [7].

f. Diagnosis

Extracellular vesicles (EV) are microvesicles that are secreted by all cells under normal or pathological conditions. EV contains cell proteins, microRNA, and nucleic acids so that it reflects the state of the cell (e.g. excretion of waste products, a signal that indicates cell damage, or as a protection mechanism). EV can diffuse through the blood brain barrier. Neuronal EV (nEV) can show the state of neurons directly. nEV containing the neurotoxic protein amyloid beta, neurofilament

light, p-T181-tau, and/or the inflammatory protein HMGB1 has been isolated from patients with HIV and cognitive impairment, Alzheimer's, and traumatic brain injury. nEV can be assessed in post-COVID patients with neurological symptoms to evaluate the patient's neurological state[16].

Conclusion

COVID-19 is a disease caused by the SARS-CoV-2 virus. This virus generally attacks the respiratory system, but through the blood it can spread to other organs. Symptoms of COVID-19 that persist for more than two weeks after infection are known as Long COVID. Neurological symptoms can occur in patients with Long COVID-19. These symptoms can include headaches, anosmia, attention disorders, ageusia, and hearing loss. The neurological symptoms of COVID-19 can be detected by looking at the nEV levels in COVID-19 patients.