ISSN 2563-9218

REVIEW ARTICLE

COVID-19 and Neurological Complications

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Koyun D. COVID-19 and Neurological Complications. Int J Biomed Clin Anal. 2022;2(2):73-78.

Abstract

Coronavirus (covid-19) infection is an acute respiratory syndrome disease that started in 2019 and spread rapidly by undergoing continuous mutation. While research on viruses continues, the modeling of covid-19 infection has begun. Thus, disorders such as encephalitis, Guillain Barre syndrome, which are neurological complications that occur as a result of acute respiratory syndrome, have been tried to be explained by the Renin angiotensin aldosterone system. In the RAAS system, ACE2 enzyme expression, which has an important role in the cell by taking on the task of exchanging substances from the outside to the inside, has been associated with COVID-19 severity and progression.

Key Words: *Virus; Covid-19; RAAS; Neurological complications; ACE2*

Introduction

During the pandemic process, which deeply affects every aspect of our lives, neurological complications associated with acute respiratory tract infection (COVID-19) have been examined. "Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)", the structure and mechanism of infection is very similar to other known coronaviruses such as SARSCoV and "Middle East Respiratory Syndrome (MERS)" [1]. The respiratory system is the most affected, but disease effects are not limited to the lung. Although it affects the respiratory tract, experimental studies and case reports raise the neurotropic effect of the virus. Neurological disorders in COVID-19 occur approximately 2 days after the onset of viral symptoms and in approximately 15% of cases [2]. The most common neurological complications in patients with COVID-19 infection were dizziness, headache, taste and sensory impairment, with a concomitant neurological finding detected in 36.4% of all cases [3]. At the same time, the complaints of COVID - 19 patients are nonspecific complaints like other respiratory infections. Fever (43-98%), cough (68-82%), fatigue (38-44%), sore throat (13.9-17.4%), dry cough (59.4%) and sputum (28-33%) are seen. The fact that the SARS-CoV-2 virus has a longer incubation period (1-14 days) causes it to infect a large number of people during the asymptomatic period. In this review, neurological complications of Covid-19 disease are discussed [4-6].

COVID-19

The Covid-19 virus, one of the respiratory infections, was first seen in Wuhan, China and

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Received: October 27, 2022, Accepted: November 28, 2022, Published: December 12, 2022

is known as severe acute respiratory syndrome.

COVID-19 (SARS-CoV-2) is responsible for the coronavirus disease declared by the World Health Organization (WHO) in March 2020 (COVID-19) [7]. On 9th November 2022, the number of deaths from covid-19 in the United States was reported as 1,070,947. In the United States, covid-19 infection has been reported as the third leading cause of death [8].

Between 21st and 27th November 2022, the overall number of cases remained stable compared to previous weeks. But 2.7 million new cases have been reported worldwide. This resulted in a 5% reduction in the number of deaths compared to previous weeks and approximately 8400 deaths were reported. Worldwide, 637 million cases and 6.6 million deaths were reported on 27 November 2022 [9].

Neurological diseases are one of the disease groups that constitute the highest health burden all over the world. Acute respiratory disease has also been added to the neurological disease area, most of which depend on chronic and well-monitored risk factors. COVID-19 can cause many different neurological symptoms and complications. Parainfectious manifestations seen during the active infection period include stroke, odor and taste disturbance, encephalopathy and encephalitis, and neuropathy and myopathies. Conditions such as headache and diarrhea are rarely observed. The main postinfectious complications are acute disseminated encephalomyelitis, transverse myelitis and Guillain-Barré syndrome, cognitive impairments and sleep disorders. It is also possible that COVID 19 may cause neurological disability in the long term. Neurological complications should be adequately known, timely recognized and effective management should be determined.

Today's pandemic, COVID-19, is one of the best examples of the threats and pressures that viruses have exerted on human health and the global economy. This outbreak has provoked an international backlash to control the spread of the virus, treat the disease and prevent future infections; The definitions of the virus, its origins, its evolution, etc. have rekindled curiosity about the virus [2,10].

Acute Cardiovascular Complication

In some patients with COVID-19 infection, acute cerebrovascular disease (VVD), other than acute respiratory syndrome complications, has been observed in approximately 1-3% of patients [11-13]. Demographic characteristics, medical history, symptoms, clinical findings, laboratory findings and chest CT findings of people who have had Covid-19 infection are recorded in electronic medical records [14]. Thus; They have been found to complain of AIS and ischemic attack (TIA) disorders [15]. However, it is understood that there are other pre-existing diseases that trigger such disorders, and that cardiac manifestations and arrhythmic complications of Covid-19 infection may be another potential mechanism that contributes to a higher rate of ischemic events in these patients. The most important mechanism, the RAAS system, contains the enzyme ACE2. The SARS-CoV-2 virus has been shown to bind to ACE2, which is found in endothelial cells of the lung, small intestine and brain vessels [14]. In this case, depletion of the ACE2 enzyme by the Covid-19 virus may cause an imbalance in the renin angiotensin system (RAS), which may cause endothelial dysfunction and subsequent ischemic events [15].

Encephalitis and Encephalopathy

Encephalitis is an inflammation of the brain, most often a viral infection. In most people suffering from encephalitis, changes in the level of consciousness, fever, seizures,

movement disorder or focal neurological deficits are observed [16,17]. Although the case of encephalitis in Covid-19 infection was also observed, this situation was based only on clinical and imaging techniques. In addition to these methods, cerebrospinal fluid (CSF) examination is also performed [18], The virus has been associated with Encephalitis disease with cases in which signs of inflammation such as protein increase and cell detection have been observed in the cerebrospinal fluid (CSF) of the virus [17]. Patients with encephalitis require multidisciplinary treatment for a long time and people with suspected brain inflammation should be controlled by a detailed examination [19].

Acute necrotizing encephalopathy (ANE) is a neurological complication that causes cytokine storming and damage to the blood-brain barrier [20]. Unlike other viral central nervous system infections, demyelination encephalopathy does not exist. A phenomenon of demyelination is the damage to the myelin sheaths surrounding the nerve cells [21]. Multifocal lesions were first shown by CT method. Later, hyper-intense signaling and internal bleeding were shown by magnetic resonance imaging (MRI) method. Of the neurological complications caused by acute encephalopathy, the thalamus, brain stem, cerebellum and cerebral white matter are the most commonly affected [20]. This has been associated with Covid-19 infection [22].

Guillain-Barre Syndrome (GBS)

Guillain-Barre syndrome has been described as the most common and severe acute paralytic neuropathy. Guillain-Barre syndrome has different clinical and pathological features of the disease [23]. Although this disorder is known as flaccid paralysis, respiratory or gastrointestinal infections, it is understood that it is caused by a virus or a bacterium. Potential trigger pathogens include viruses (Cytomegalovirus (CMV), Ebstein-barr virus (EBV), influenza virus, hepatitis E virus, Zikavirus, etc.) and bacteria (C. Jejuni, M. Pneumoniae, etc.) [24]. When the data were examined in Covid-19 patients, upper respiratory tract infection was detected 5 to 14 days before the development of symmetrical weakness, and then respiratory failure was observed [25,26]. In Guillain-Barre syndrome, cerebrospinal fluid (CSF) analysis is performed and the CSF method usually shows high protein. However, this height is not evident until the third week of the disease. Therefore, early and good diagnosis is important in this disease [27,28].

Hemophagocytic Lymphocytosis (HLH)

In the Covid-19 infection outbreak, some individuals carry symptoms of acute respiratory distress and flu; hemophagocytic lymphocytocytosis (HLH) has been observed in some intensive care patients. As a result of excessive activation of cells such as HLH, t-lymphocytes, natural killer cells and macrophages, a severe dysregulation caused by multi-organ injury with a large cytokine storm has been observed. This condition is usually secondary to hematological malignancy (a disorder due to the formation of malignant blood disease by showing an uncontrolled proliferation of cells), immunosuppression (discomfort caused by different reactions of patients to drugs) or critical infection, but has been described in Covid-19 infectious patients [29]. HLH patients have unremitting fever, pancytopenia (the number of red blood cells, white blood cells and platelet cells has stopped decreasing), coagulopathy (a condition that causes platelet blockages as a result of clotting in the vein), hepatic dysfunction (liver disease), hypertriglyceridemia (high triglycerides in the blood) and high ferritin (an intracellular protein that stores iron and releases serbet in a controlled way) [30-32]. HLH is a little-

known neurological complication of HLH among COVID-19 patients. Because of the innate immune system, IL-2 (which causes cytolytic activation, which is a natural killer cell), IL-6 (B plays a role in lymphocyte proliferation and differentiation / causes fever), IL-7 (hemotopoietic, that is, plays a role as a growth factor of blood cells) and TNFα (plays a role in intravascular clotting) levels increase significantly and cause cytokine storm [33-36]. This means that COVID-19 patients with HLH have been observed to develop neurological abnormalities at a certain rate [31].

Drug Interactions

Most of the drugs recommended for Covid-19 infection have significant drug interactions and side effects. The drugs used in Covid-19 infection also pose a risk of neurocognitive impairment [37-39].

1. **Azithromycin:** It is a macrolide group antibiotic used in the treatment of Gram positive cocci. In vitro and preliminary clinical trials have shown that hydroxychloroquine alone or in combination with azithromycin (hydroxychloroquine + azithromycin) may be effective in treating COVID-19.

2. **Remdesivir (GS-5734):** Adenosine nucleotide analogue that inhibits RNA polymerase is an example of a broad-spectrum antiviral. The use of remdesivir in COVID-19 has been demonstrated in several case series.

3. **Lopinavir (8200 mg)/Ritonavir (50 mg):** It is an aspartate protease inhibitor agent used in the treatment of HIV infection. In a randomized controlled trial, lopinavir/ritonavir treatment did not show any benefit beyond standard care in hospitalized adult patients with severe COVID-19.

4. **Hydroxychloroquine / Chloroquine:** Hydroxychloroquine, which has a chemical structure very similar to chloroquine, is used in the treatment of malaria and rheumatic diseases. It has been proven to have strong antiviral activity against SARS-CoV in cell cultures and animal studies [40,41].

Conclusion

There are various limitations in the case reports, potential risks, effects on patients and their comparison obtained in the literature reviews on neurological complications due to Covid-19 infection and their effects on individuals. However, as a result of observations and studies on some patients, it has been observed that the Covid-19 infection outbreak causes potential neurological complications such as acute cerebrovascular, encephalitis, encephalopathy, guillain barre syndrome, hemophagocytic lymphosphocytosis. Even in some drug methods used for therapeutic purposes, there is a risk that the individual who is sick may also interact with the disorders that occur with pre-existing neurological complications. This can cause the sick individual to worsen. Therefore, the treatment of a person who comes with the complaint of Covid-19 infection should be done in a controlled and careful manner by specialist physicians by taking precautions against any complications that may occur.

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