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Chapter

COVID-19 Pandemic and Neurocognitive Process: New Scenarios for Understanding and Treatment

Serefnur Ozturk and Fettah Eren

Abstract

COVID-19 disease was defined as a disease of primary respiratory system. However, symptoms associated with central nervous system were detected in approximately 2/3 of the hospitalized patients. The rate of ischemic cerebrovascular diseases is higher in central nervous system. In addition, hemorrhagic cerebrovascular diseases, encephalitis and/or encephalopathy are the other diseases. Complex pathogenesis was demonstrated in the central nervous system diseases associated with SARS-CoV-2. It was reported that SARS-CoV-2 virus could directly invade the central nervous system, especially via the olfactory nerves or the haematological pathway. As a result, endothelial cells, pericytes and/or neurons can be infected (direct pathway). Another mechanism is central nervous system deficit resulting from peripheral immune reactivation (indirect pathway). All these etiopathogenetic results support that COVID-19 disease is associated with cognitive dysfunction. Cerebral hypoperfusion associated with vascular endothelial structures is the main factor in the etiopathogenesis. It was reported that COVID-19 disease induced amyloid-β (Aβ) and α-synuclein phosphorylation. Besides, it was detected that this process was associated with tau and TDP-43 pathology. "Cognitive COVID-19" is a term that describes acute and long-term cognitive changes in people infected with SARS-CoV-2. Encephalopathy, delirium and cognitive disorders are most frequently detected. In this chapter, the clinical and etiopathogenetic processes of cognitive dysfunction after COVID-19 disease were evaluated. In addition, the disease, disease process and treatment were evaluated in general.

Keywords: COVID-19 disease, SARS-CoV-2 infection, pandemic, cognitive function, neurocognitive disorder

1. Introduction

Coronavirus disease 2019 (COVID-19) was initially defined as a disease that only causes respiratory system infiltration. However, in addition to major respiratory system symptoms, some systemic and neurocognitive symptoms were also detected in

the acute or subacute/chronic period [1]. In these studies, the sample size and clinical and sociodemographic characteristics of the patients were heterogeneous. Therefore, the relationship between COVID-19 disease and neurocognitive dysfunction could not be determined definitively. Recent studies confirmed this relationship. Based on these results, the disease was named "infectious disease-associated encephalopathy" or "Cognitive COVID [2]." Neurological deficits associated with COVID-19 disease were investigated in the several studies. Cognitive deficits were detected more frequently in the post-hospitalization period associated with COVID-19 disease [2–4]. In addition, severe cognitive impairment was observed in some patients with COVID-19 [5, 6].

Nonspecific encephalopathy symptoms (headache, confusion, delirium, disorientation, etc.) were detected in 25% (53/214) of hospitalized patients [7]. This rate is higher in studies reported from Europe. Neurocognitive disorders and psychosis were detected 69% in studies from France and 31% from the United Kingdom (UK) [8, 9]. In a recent study, inattention and disorientation were detected at a frequency of 33% after hospitalization in patients with COVID-19 disease [8]. Micro-structural changes and functional disorders were reported during 3-month follow-up of COVID-19 patients. [10]. These results demonstrate that COVID-19 disease causes structural and functional changes in the brain over a long period.

Previous studies have emphasized that the pathogenesis of encephalopathy associated with infection is different from non-infectious encephalopathy. In the literature, there are some studies on the effects of influenza A virus subtype H1N1 (A/H1N1) virus and severe acute respiratory syndrome coronavirus (SARS-CoV) virus on the central nervous system. However, scientific data regarding the etiopathogenesis of cognitive impairment are insufficient [2, 3]. Many mechanisms were reported about the acute, subacute and chronic effects of the SARS-CoV-2 virus. The first mechanism is viral neurotropism. The second mechanism is the general systemic inflammation and secondary effects of cytokine storm. The rates of acute and chronic cognitive dysfunction are higher in patients with acute respiratory distress syndrome (ARDS) and mechanical ventilation [4]. The third mechanism is neurocognitive dysfunction associated with psychosocial isolation. Pandemic-related social isolation and increasing death rates have revealed neurocognitive and neuropsychiatric symptoms over a long period [3, 11]. Evaluating the mechanisms and results of this process is important for the disease and possible treatment strategies.

COVID-19 disease affects the central nervous system with vascular and parenchymal deficits. Many cases of encephalopathy associated with COVID-19 have been reported without cerebral lesions [12]. Patients with neurological clinical symptoms are older and have more severe respiratory symptoms [7]. It is known that SARS-CoV-2 infection directly affects the central nervous system. It also produces indirect neurotoxicity with systemic immune hyperinflammation [13]. Infections damage the endothelium in cerebral vascular structures as well as systemic vascular endothelial structures and blood-brain barrier (BBB). As a result, neurological symptoms are associated with this neuroinflammatory process [14]. Previous studies have reported a relationship between chronic infection and hippocampal atrophy [15]. These results support the relationship between infections and cognitive dysfunction.

Patients with severe respiratory symptoms should be frequently evaluated for neurocognitive dysfunction during the COVID-19 disease process. Particularly, patients with cerebrovascular disease and other neurological complications should be evaluated more frequently. Detailed cognitive evaluation including long-term neurological and psychiatric symptoms should be performed on these patients. We aim to evaluate

"Cognitive COVID" and its neuropathological process in this chapter. In addition, we aim to discuss the clinical features and etiopathogenetic process of the disease with the current literature and to present the results associated with treatment.

2. Neurocognitive impairment in the previous coronavirus outbreaks

Two major coronavirus outbreaks were reported before the SARS-CoV-2 infection. These outbreaks were acute respiratory distress syndrome (ARDS) associated with SARS-CoV and Middle East respiratory Syndrome (MERS) associated with MERS-CoV virus [6, 16]. Neurocognitive disorders during the COVID-19 pandemic process have often been compared with these outbreaks. It has been reported that neurocognitive impairment is dominant in the COVID-19 process. These results were explained by the psychosocial effect of the disease and social isolation [12]. However, neurocognitive impairment is not only associated with psychosocial processes. Because the induced systemic inflammatory process contributes to neurocognitive dysfunction [14]. In a study of MERS-CoV patients, confusion was indicated to be associated with magnetic resonance imaging (MRI) results [17]. It was reported that approximately 25.7% of the patients had confusion [18].

Confusion, neurocognitive and neuropsychiatric symptoms are not only present in coronavirus infection. Inattention, memory and learning defects have been reported in human immunodeficiency virus (HIV) and Zika virus (ZIKV) diseases [19, 20]. Influenza virus may also cause cognitive dysfunction. The clinical presentation of the disease may progress from mild cognitive impairment to seizure and/or severe encephalopathy [21]. Influenza-associated neurological clinical manifestation is not common compared to coronavirus. In a national study conducted in Malaysia, the rate of neurological manifestation was detected as 8.3%. The hospitalization rate is higher in this patient group. However, long-term cognitive deficits are rare in patients with influenza [21, 22].

3. Neuropsychiatric and neurocognitive effects of the disease in the acute and chronic periods and its clinical manifestations

During the COVID-19 pandemic, social restrictions and the fear of contact with a COVID-19 patient have created a serious social panic. This is a cause for many psychological disorders [11, 23]. Anxiety and depression are the most common psychiatric disorders in this process [24]. In some studies, it has been demonstrated that the incidence of post-traumatic stress disorder (PTSD) is between 7 and 53.8% during the pandemic process [25]. Especially in elderly patients, cognitive dysfunction is associated with social isolation and psychological disorder [26]. In a recent population-based study, the effect of psychological stressors on the general cognitive functions of the population was evaluated. The results demonstrated that these factors cause cognitive dysfunction. In addition, it has been demonstrated that the psychological disorders associated with the pandemic are induced by anxiety and depression [27].

Cognitive disorders after viral infections have a complex presentation [12, 28]. There are some publications about neurocognitive effects of the COVID-19 pandemic. Acute impairment in neurocognitive functions during the COVID-19 disease is associated with metabolic disorder. Other neuropathological mechanisms are

neurotropism of SARS-CoV-2, mechanical ventilation and adverse effect of neurosedative treatments [29].

In a study during the initial period of the pandemic, many neurological symptoms have been reported in patients with COVID-19. Dizziness, headache and neurocognitive deficits were detected in 24.8% of the patients [7]. In a study reported from the UK, behavioural and cognitive impairments were detected in 31% of the patients. Major neurocognitive disorders were determined in approximately 5% of total patients. Some cases of acute viral encephalitis have been reported during or after COVID-19. Transient or persistent neurocognitive disorders were determined in patients with encephalitis [3, 30]. These symptoms are called dysexecutive syndrome. Approximately 25% of COVID-19 patients presenting with ARDS had dysexecutive syndrome. Executive dysfunction predominates in these patients [8, 31]. It has been reported that neurocognitive disorder symptoms are more common in the elderly patients with severe respiratory/systemic symptoms [3]. Many mental disorders have been reported in the acute or chronic period of COVID-19 disease. In addition, post-infection cognitive disorders continue with long-term inattention and memory problems.

The long-term effects of COVID-19 disease were investigated in some studies. In a study by Woo et al., cognitive functions of COVID-19 patients were evaluated after being discharged from the intensive care unit. A lower cognitive function score was detected in the patients. More than one cognitive disorder, such as inattention (50%) and memory disorders (44.4%) was detected [32]. Lu et al. evaluated 60 patients during the early stage of SARS-CoV-2 infection and at a 3-month follow-up. Cognitive impairment increased during the process in this study [33].

4. Pathophysiology of neurocognitive disorders in COVID-19

The pathophysiological mechanisms of neurocognitive impairment after COVID-19 disease have not been determined definitively. SARS-CoV-2 infection causes deficits in the central nervous system by direct and/or indirect mechanisms. The induced psychosocial process contributes to neurocognitive dysfunction. This disease is a complex process with vascular and metabolic disorders. All factors associated with neurocognitive dysfunctions are summarized in **Figure 1**. There are 4 main pathophysiological mechanisms in this process. They are vascular, inflammatory, psychosocial factors and direct neurotropism.

4.1 Cerebrovascular diseases

The risk of acute cerebrovascular disease increased in COVID-19 disease after SARS-CoV-2 infection. In studies, cerebrovascular disease was detected with a frequency of 2–6% in hospitalized patients with the diagnosis of COVID-19 [12]. In a study reported from Spain, stroke was determined in 23 (1.4%) of 1683 patients. Approximately 75% of stroke patients were ischemic stroke [34]

It has been detected that cerebrovascular diseases are more common in COVID-19 patients with neurological complications. The incidence of stroke is higher in elderly patients with severe disease activity. This rate is higher, especially in patients with comorbid diseases, such as hypertension, diabetes mellitus and cerebrovascular disease [30]. However, stroke associated with large vessel disease after COVID-19 disease may be detected in young adults [35].

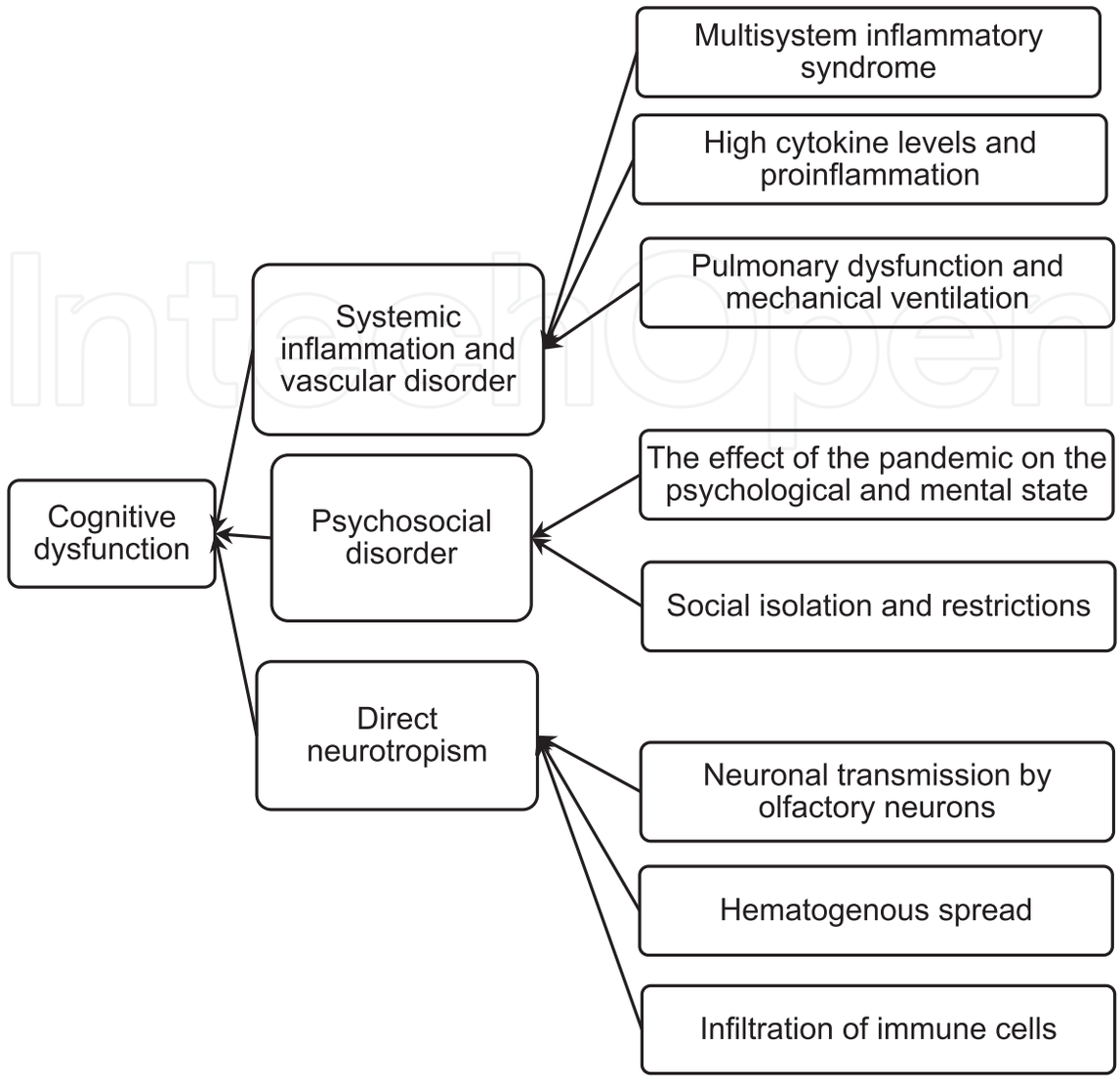

Figure 1.
Possible causal factors of cognitive symptoms associated with COVID-19 (coronavirus disease 2019).

Neurocognitive disorders associated with cerebrovascular diseases occur in COVID-19 patients. The pathophysiological mechanism of this process has not been definitively defined. This process is associated with systemic inflammation and disseminated intravascular coagulation (DIC) [36]. In patients with ARDS associated with COVID-19, a series of reactions including endothelial cell dysfunction, vascular leakage and dysregulated immune activation have been demonstrated for the mechanism of DIC. Activation of kallikrein-bradykinin system, leukocyte adhesion molecules, platelets and neutrophils increase inflammation. This process potentially causes vascular and neuronal damage in patients with COVID-19. SARS-CoV-2 infection damages vascular endothelial structures in cerebral vascular and many other tissues [37]. In many studies, major neurological complications after COVID-19 disease have been associated with cerebral vascular injury and ischemia.

Postmortem neuropathological autopsy studies in COVID-19 patients identified acute hypoxic-ischemic brain injury and perivascular inflammation in the cerebrum and cerebellum. However, SARS-CoV-2 virus could not be isolated in the central nervous system [38]. In the early postmortem period, hemorrhagic lesions and evidence of posterior reversible encephalopathy syndrome (PRES) were detected in patients with COVID-19 [39].

The results of the studies describe that COVID-19 process causes deficits in the central nervous system. The pathophysiological mechanisms of neurocognitive dysfunction in COVID-19 disease are systematically summarized in **Table 1**. It has been demonstrated that brain damage and cognitive impairment are associated with ischemic and inflammatory processes. Cognitive dysfunction associated with hypoxic-ischemic brain injury is explained by these mechanisms.

4.2 Systemic inflammation and acute respiratory distress syndrome

During the COVID-19 disease process, cytokine storm causes severe systemic inflammation [14]. Increased interleukin-1 (IL-1) and other mediators in the systemic circulation are major factors in systemic inflammation associated with COVID-19 [40, 41]. Increased proinflammation causes a vasculitic process, impaired capillary permeability and diffuse vascular thrombosis. This process causes damage to the blood-brain barrier. In addition, microglial inflammation is activated [42]. Neurological symptoms occur as a result of all these mechanisms. In the early period, delirium and seizures have been described [3]. Besides, increased inflammation may be associated with cerebrovascular diseases. As a result, a cerebral hypoxic-ischemic process is induced [5]. The possible causal elements of inflammatory factors on cognitive symptoms associated with COVID-19 disease are figured (**Figure 2**).

It is known that there is a relationship between cognitive disorders and increased inflammation. In a study evaluating Alzheimer's patients and the control group, a correlation was detected between cognitive impairment and increased systemic inflammation [43]. Long-term cognitive dysfunction is more common in patients with severe inflammatory disease. In addition, neurocognitive dysfunction associated with inflammation is higher in patients with neurodegenerative disease [44, 45].

The relationship between C-reactive protein (CRP) level and cognitive dysfunction was investigated in patients with COVID-19 disease. A positive correlation was determined between increased CRP level and cognitive impairment [46]. These

No.	Factor	Mechanisms
1.	Cardiorespiratory failure	Cerebral hypoperfusion Hypoxic-ischemic brain injury Diffuse white matter damage
2.	Coagulation disorder	Cerebral artery thrombosis Disseminated intravascular coagulation
3.	Cerebral microvascular dysfunction	Endothelial damage Pericytes damage Blood-brain barrier leakiness Neurovascular dysfunction Impaired autoregulation Impaired vascular/para-vascular drainage
4.	Renin-angiotensin system (RAS) dysregulation	RAS dysregulation RAS signal hyperactivity
5.	Encephalitis	Neuroinvasion via olfactory nerve Indirect inflammatory or vascular system

Table 1.
The pathophysiological mechanisms of neurocognitive dysfunction in COVID-19 disease.

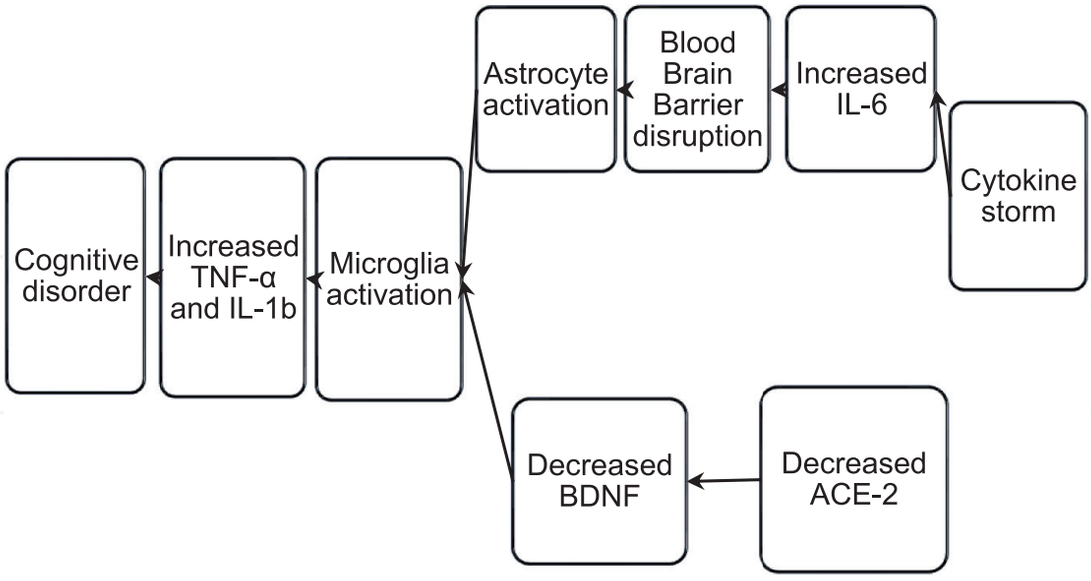

Figure 2.
The possible causal elements of inflammatory factors on cognitive symptoms associated with COVID-19.

results were evaluated in another study. The relationship between CRP levels and cognitive impairment was confirmed. In the same study, the relationship between cognitive dysfunction and CRP level was also demonstrated over a long period. Disease-related respiratory failure and hypercapnia are the causes of increased IL-1 levels. These results are associated with cognitive impairment [47].

In a study from China with a large patient population, hospitalization was indicated in 19% of COVID-19 patients. In addition, ARDS was detected as a major indication for hospitalization associated with COVID-19 disease [48]. Post-ARDS cognitive impairment is not only associated with COVID-19 disease. Other diseases can also cause cognitive impairment after ARDS [49]. Neurocognitive impairment after ARDS is associated with hypoxia, induced hyperinflammation, and hemodynamic instability. Meta-analyses and studies have reported that neurocognitive dysfunction after ARDS has a high incidence. The incidence of neurocognitive dysfunction is 70–100% at the time of hospital discharge, 46–80% one year after discharge and 20% five years after discharge [49]. In addition, mechanical ventilation without ARDS is associated with long-term cognitive dysfunction and poor quality of life. Sedative treatments for mechanical ventilation are also associated with long-term cognitive impairment [50]. The evidence for the isolation of the virus directly from the cerebrospinal fluid (CSF) is insufficient [14]. There is a relationship between all these pathophysiological mechanisms. These mechanisms are complex and they create cognitive dysfunction.

4.3 Direct neurotropism

The investigations are limited about the direct invasion of the SARS-CoV-2 virus to central nervous system. However, it is thought that SARS-CoV-2 may invade neuronal tissue similar to other coronaviruses [51, 52]. Rare investigations have reported evidence of SARS-CoV-2 in the CSF examination [30, 53]. There are some mechanisms for the invasion of the virus (SARS-CoV-2) into the central nervous system However; these mechanisms are not definitive evidence. All mechanisms are explained in 3 main pathways.

The first pathway is direct retrograde neuronal transmission via olfactory neurons. It is known that the sense of smell and taste associated with SARS-CoV-2 is reduced. This is the first symptom of the disease in some COVID-19 patients. The smell impairment is explained by direct invasion of the mucosal epithelium and olfactory nerves [54]. Direct invasion is associated with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors. SARS-CoV-2 has a high affinity for ACE2 receptors [55]. Experimental studies about SARS-CoV confirmed neuronal transmission to the brain via the olfactory bulb. Structural and/or functional changes associated with COVID-19 have been reported in several areas of the brain (entorhinal cortex and hippocampus). Neuronal dysfunction associated with this process has been demonstrated [24].

The second pathway is hematogenous spreading. Some researchers report that the virus may cause cognitive disorders by direct hematogenous spread via the cerebrovascular pathway [5]. There is some data that SARS-CoV-2 has been detected in the blood samples of some COVID-19 patients. Functional (ACE2) receptors of SARS-CoV-2 are higher in endothelial cells and pericytes [56, 57]. The interaction of the virus with these receptors is the first step towards neuronal dysfunction. Delayed neurotropic features of SARS-CoV-2 induce major etiopathogenetic mechanisms for cognitive deficits and neurological symptoms [3]. Induced interleukins, tumour necrosis factor (TNF) and other inflammatory cytokines associated with SARS-CoV-2 may disrupt the endothelial structure of the blood-brain barrier [58]. This process contributes to a major neuroinvasion.

The third pathway is immune-mediated neuronal spreading. In a SARS-CoV-related study published in 2005, it was demonstrated that viral particles were detected in monocytes and lymphocytes [59]. Immune system cells may cause direct brain damage via ACE-2 receptors [60]. However, direct immune cell infiltration was not detected in the brain with pathological investigation after autopsy [60].

5. The relationship between COVID-19 vaccination and cognitive functions

Major neurocognitive disorders are higher in the elderly population. This disease is higher in patients over 60 years old, especially over 80 years of age. In addition, this age group is more sensitive to infections. Immune dysregulation causes a decreased vaccine-associated immune reaction in these patients. Increased age is associated with decreased immunity and increased risk of complications. International investigations have been initiated to accelerate the development of vaccines and medications for the COVID-19 pandemic. These results suggest a different vaccination protocol, especially with increased age. Because this group is highly sensitive to major neurocognitive disorders and other diseases [61].

More cases of adverse reactions after COVID-19 vaccination are being reported. One of the adverse reactions is neurocognitive disorders after vaccination. However, neurocognitive disorders are lower after COVID-19 vaccines. In a recent case report, two cases of encephalopathy were reported within one week after mRNA vaccination [62]. In addition, delirium was reported in an 89-year-old patient after the first dose of the mRNA vaccine [63]. The mechanism of the disease is systemic inflammation associated with anti-spike antibodies and macrophage activation after mRNA vaccines [62–64]. However, there is no case-control study on this subject.

Most of the immunogenic epitopes of SARS-CoV-2 are similar to human proteins. Vaccines with these epitopes have more risk for autoimmunity [65]. Increased inflammation and biochemical reactions associated with autoimmunity can cause neuroinflammation and cognitive impairment [66]. Experimental studies have demonstrated that there is a relationship between increased autoimmunity and cognitive impairment [67]. However, all these evaluations demonstrate that there is no definite relationship between vaccination and cognitive dysfunction.

6. Etiopathogenetic evaluation for understanding and treatment of the disease

It is important to know the causality and etiopathogenesis of COVID-19-related cognitive impairment before the treatment phase. All mechanisms are explained in 3 major pathways. The first is the direct neurotropism of SARS-CoV-2 and is explained by past SARS-CoV studies. The virus may invade the brain by direct neuronal or indirect immune cells-mediated hematogenous pathway. One of the main steps of treatment is to prevent the infiltration of virus-infected immune cells into the central nervous system. It is aimed to prevent cytokine storm with immunosuppression treatment. However, it is important that immunosuppression therapy does not induce infection. The second important step is to prevent the invasion of infiltrating cells with SARS-CoV-2 into the impaired blood-brain barrier structure. At this stage, it should be aimed to stabilize the blood-brain barrier structure [57, 58]. The main aim of treatment is to prevent immune reactivation. Viruses can cause retrograde brain invasion via olfactory neurons. However, there is not enough data about this subject. Invasion has been demonstrated to be associated with ACE2 and TMPRSS2 [12]. Therefore, these proteins and receptors should be targeted in therapy to prevent direct neuronal invasion [12]. Therefore, these proteins and receptors should be targeted during the treatment phase to prevent direct neuronal invasion.

Increased hyperinflammation is detected after cytokine storm in patients with COVID-19. Cytokine storm causes systemic inflammation and vascular damage. Thus, over-induced neuroinflammation is triggered. In addition, mechanical ventilation, cardiopulmonary failure and hypoxia also induce the neuropathological process. Prevention of hypoxia and increased proinflammation is important in the prevention of cognitive impairment. As a result of these mechanisms, cerebral microvascular dysfunction is tried to be prevented [57, 58].

Neuropsychiatric factors have been demonstrated to be important in the pathogenesis. Evaluation of neuropsychiatric disorders in the treatment phase is one of the main strategic steps. Therefore, all patients with and without neurological diseases should be evaluated for neuropsychiatric diseases. The major neuropsychiatric disorders in the COVID-19 disease process are anxiety and depression. These diseases should also be treated [6, 45, 68]. Evaluation of psychiatric and neurocognitive status is important in these patients.

The most important step of this process is the prevention of viral transmission. SARS-CoV-2 spread primarily via respiratory droplets during close face-to-face contact. Personal hygiene, social distance (at least 1 meter, optimum 2 meters) and personal protective equipment are important for protection from COVID-19 disease [57].

Neurocognitive disorders associated with coronavirus infection may have iatrogenic aetiology. Favipiravir and hydroxychloroquine are safe drugs for cognitive

dysfunction. No cognitive impairment has been reported as an adverse reaction to tocilizumab. Azithromycin may cause somlonans, insomnia or agitation [57].

7. Approach to cognitive disorders in COVID-19 disease

The primary cause of cognitive impairment and the etiopathogenetic process should be investigated in patients with COVID-19. It is important to investigate systemic and metabolic causes. Activation of the renin-angiotensin system may also impair the metabolic process. Therefore, patients should also be evaluated for endocrinological status [69, 70]. Cardiopulmonary failure and hemodynamic disorders that cause cognitive impairment should be evaluated in patients with COVID-19. Hypoxic ischemic brain injury and diffuse white matter injury associated with hypoxemia are important for treatment and etiopathogenetic process [38, 39, 57].

Hypercoagulability-related cerebrovascular disease should be considered in COVID-19 patients with acute neurological clinical symptoms. Ischemic stroke in a COVID-19 patient is associated with indirect intravascular coagulation or direct cerebral arterial thrombosis after DIC [36, 71]. Brain neuroradiological imaging is indicated for these patients (Computed tomography (CT) and/or magnetic resonance imaging (MRI)).

Encephalitis may be detected as a result of direct or indirect neuronal invasion in patients with COVID-19. In these patients, diffusion restriction in the central nervous system, particularly in the corpus callosum splenium, has been reported. Patients usually have encephalopathy and neurocognitive symptoms. The neurological examination should be repeated periodically. CT and/or MRI neuroimaging is required. Electroencephalography (EEG) and CSF examination should be performed in some patients [3, 72, 73].

Hyperactive delirium is more common than hypoactive delirium in COVID-19 disease. Treatment and management of this clinical symptom are difficult. Scales associated with cognitive dysfunction and delirium should be applied periodically during the COVID-19 process. Control of risk factors associated with this process, optimum blood oxygenation, fluid and calorie support and cognitive behavioural therapy are important [2, 42].

It should be recommended not to change the living environment of patients during the COVID-19 disease process. Chronic diseases, alcohol and drugs may precipitate cognitive dysfunction. Therefore, it is important to evaluate these factors. Anticholinergic adverse effects of treatments for COVID-19 disease should be evaluated. In addition, anticholinergic adverse effects of treatments for chronic diseases should be evaluated [57, 74]. Agitation and cognitive changes are treated with haloperidol and benzodiazepines. However, these treatments have the potential for respiratory depression and extrapyramidal adverse reactions.

8. COVID-19 pandemic and major neurocognitive disorder

The COVID-19 pandemic has different effects on patients with Alzheimer's disease and other major neurocognitive disorders. These effects are not only associated with SARS-CoV-2 infection. On the other hand, the psychosocial process of the pandemic process also has negative effects. In some clinical studies, patients with major

neurocognitive disorder and non-major neurocognitive disorder have been compared. Patients with major neurocognitive disorders have higher risk for COVID-19 disease. There are many etiological risk factors for the COVID-19 disease in patients with major neurocognitive disorder. First, cognitive impairment and neuropsychiatric symptoms are common in patients with major neurocognitive disorders. Therefore, protective factors and their management are difficult in patients with COVID-19 [75]. Moreover, it is not possible for these patients to fulfil the requirements of quarantine.

The potential for the APOE ε4 genetic allele is higher in patients with major neurocognitive disorders. This condition damages the blood-brain barrier and precipitates cognitive dysfunction. It is also known that APOE ε4 induces cognitive dysfunction associated with microglia. This process produces neuroinflammation and neurodegeneration [76]. In addition, APOE ε4 is associated with increased cytokine after inflammation. Cytokine storm is induced by these mechanisms. Cytokine storm is directly associated with serious COVID-19 disease complications, such as lung injury and multi-organ failure [77].

There are severe individual and social isolation precautions in many countries to control the pandemic. Pandemic precautions are higher in patients with major neurocognitive disorders. This situation causes neuropsychiatric effects. Especially social isolation causes serious psychiatric symptoms in this patient group. In addition, the incidence of stress, anxiety and depression has increased [75–78]. Social isolation is higher in patients with major neurocognitive disorders in the care centres. Therefore, these patients have more exposed to neuropsychiatric and neurocognitive effects. This is one of the reasons for increased neuropsychiatric symptoms in patients with major neurocognitive disorders [75, 76]. Social isolation in patients with major neurocognitive disorders has been associated with neuropsychiatric and neurocognitive disorders.

Social isolation causes more agitation and cognitive impairment in major neurocognitive disorder patients than in other patient groups. The neurocognitive dysfunction correlates with the duration of social isolation. Neurocognitive dysfunction, especially in the quarantine period, may be permanent. Older patients with major neurocognitive disorders have higher risk for COVID-19 disease. These patients have more severe disease outcomes than other patients without major neurocognitive disorders [79–81]. A large-scale cohort study in the UK has demonstrated that patients diagnosed with major neurocognitive disorders are at three times higher risk for severe COVID-19 disease than other patients [80]. Risk factors for major neurocognitive disorders – age, obesity, cardiovascular disease, hypertension and diabetes mellitus – are also risk factors for SARS-CoV-2 infection and severe COVID-19 disease [81]. Some genetic risk factors for COVID-19 have been determined. In particular, a study reported from the United Kingdom demonstrated that homozygous genetic mutations for APOE ε4 are a risk factor for hospitalization associated with COVID-19 [82].

In summary, the pieces of evidence demonstrate that: First, older patients with major neurocognitive disorders are at higher risk for COVID-19 disease. These patients are also at higher risk of disease-related morbidity and mortality after COVID-19 infection. Second, major neurocognitive disorder patients were isolated for a long period to control SARS-CoV-2 infection. These patients have a higher risk for neuropsychiatric and severe neurocognitive disorders. Consequently, social networks, occupational therapy, caregivers and staff education are important during and after the pandemic in patients with major neurocognitive disorders.

9. Conclusion

There are limited studies about cognitive dysfunction in COVID-19 disease in the literature. However, the negative effects of the pandemic have decreased. There is some evidence about the long-term cognitive effects of the COVID-19 disease in the literature. Therefore, it is necessary to plan more investigations about cognitive dysfunction and COVID-19 disease. Understanding the etiopathogenesis is important for diagnosis and treatment modality.

All results demonstrate that it is not possible to explain "cognitive COVID-19" with a single scenario. Etiopathogenesis has multifactorial effects. The disease has a complex nature. Understanding the disease and its treatment is not easy. This complex interaction makes it difficult to determine a single cause or effect. Understanding the etiopathogenesis of this process will decrease the risk of "cognitive COVID-19." It is known that most of this process is at the micromolecular part with inflammatory mechanisms. In addition, interactions at the receptor level are also important in this process. Therefore, determination of the etiopathogenetic process is essential for detection of treatment options.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Serefnur Ozturk* and Fettah Eren
Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey

*Address all correspondence to: serefnur@yahoo.com

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