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Neurocognitive Manifestations of SARS-CoV2: A Narrative Review of Mechanisms

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Abstract
Since the outbreak of COVID-19 that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020 throughout the world, a lot of aspects of people's lives are affected including their psychological status. Follow-up assessment of survivors of this infection showed that they had multiple psychological disorders including depression, panic attacks, obsessive compulsive disorder, and post-traumatic stress disorder. It is estimated that more than one-third of patients with COVID-19 experience neuropsychiatric symptoms, including headache, paresthesia, and disturbed consciousness. Among patients affected by COVID-19, there are different mechanisms that can cause cognitive dysfunction. COVID-19 can affect the central nervous system (CNS) directly by invasion and indirectly by inducing hypoxia, inflammation, and delirium. The pandemic and fear of infection can also cause anxiety which impairs the cognition as well. By assessing the patients' cognition and knowing the higher probable cause of cognitive impairment, we can form a better strategy to better treat the impairment. Cognitive behavioral therapy can be effective in reducing the anxiety and cognitive rehabilitation therapy (CRT) can be used to lower the detrimental effects of cognitive impairment caused by COVID-19.
Keywords: COVID-19; Cognitive dysfunction; Anxiety; Depression; Delirium; Inflammation; Hypoxia.

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Introduction

Since the global outbreak of COVID-19 that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020, a lot of aspects of people's lives are affected including their psychological status.[1] Neurological manifestations of COVID-19 can be divided into those affecting the central nervous system (dizziness, ataxia, stroke, encephalitis, demyelination) and those affecting the peripheral nervous system (anosmia, agnosia, Guillain barre syndrome).[2,3]

It was previously shown that viral diseases affecting the respiratory system can cause psychological outcomes that may last for a short or long time.[1] Follow-up assessment of survivors of SARS-Cov-2 infection showed that they had multiple psychological disorders including depression, panic attacks, obsessive compulsive disorder, and post-traumatic stress disorder.[4] Their risk of suicide and psychosis were significantly higher especially until one year of testing positive for SARS.[5] Recently, there is a focus on the neuropsychiatric presentations of COVID-19. It is estimated that more than one-third of patients with COVID-19 experience neuropsychiatric symptoms, including headache, paresthesia, and disturbed consciousness. Neuropsychiatric symptoms usually are associated with a more serious form of disease.[6] Recent studies show that patients affected by COVID-19 may show cognitive impairments like delirium. Their mood may be also affected by COVID-19 by direct and indirect mechanisms and depression, anxiety and insomnia may be prevalent in these patients.[7] Besides biological mechanisms such as positive neurotropism of virus immunological and inflammatory responses, the fear of dying due to the respiratory infection and social isolation, poses a great risk for getting anxiety and panic disorder that may impair cognition[8,9] In this review we aimed to investigated the mechanisms through which COVID-19 can produce psychological disorders that causes cognitive impairment and propose treatment options to decrease

the psychological burden and cognitive impairment of the disease.

Delirium

As little is known about the central nervous system (CNS) manifestations of COVID-19, the mechanism of delirium in the patients affected by COVID-19 may not be fully understood. Taking into consideration the severity of illness and ICU admission with the possibility of intubation, it is not out of mind that COVID-19 would cause delirium especially in the older adults with underlying conditions and previous cognitive impairments.[10]

Hence delirium in COVID-19 should be considered as a primary and secondary cause. In the primary hypothesis it is presumed that COVID-19 can target the brain directly but in the secondary hypothesis it is regarded that the delirium is caused by exacerbating the underlying conditions, the electrolytes imbalance and ICU admission.[11] In a case series of 58 patients admitted in the intensive care unit (ICU) because of COVID-19 infection, 65% had significant scores in the confusion assessment method for the intensive care unit (CAM-ICU) and 84% of them had neuropsychiatric presentations. Agitation were present in 69% of patients which needed additional sedation.[12] In a study on the discharged patients after 4 weeks, cognitive tests were done by telephone. The patients who had delirium during admission had significantly lower cognitive scores.[13]

In a case series that investigated the conditions of patients with delirium in COVID-19 units, all the patients had an objective or subjective cognitive impairment but this report cannot rule out the potential effect of COVID-19 neurotropism as an underlying cause of delirium.[11] Some coronavirus can infect the brain by connecting to the medullary cardiorespiratory center and induce respiratory failure. By this mechanism coronavirus can both cause delirium directly by infecting the brain and indirectly by inducing brain hypoxia.[14] Another access route to the brain is the olfactory bulb. This finding is consistent with high rates of anosmia in the patients with COVID -19. The virus goes up to the uncinate fasciculus and anterior cingulate gyrus.[15] Interestingly the dysosmia is also common in the patients with Parkinson's disease, Alzheimer's disease and systemic lupus erythematous (SLE).[16] In patients with SLE, the severity of anosmia correlates with the disease activity.[17] The relationship between the severity of anosmia and disease severity of COVID-19 is not studied that can be a field of research for further studies.

It should be considered that inflammation caused by the virus can also exacerbate the delirium in affected patients. Patients critically affected by COVID-19 who need ICU care, are at an impending risk of advanced delirium which can be aggravated with using sedatives and previous medical comorbidities especially in the elderly.[18]

Encephalitis

A case series from Wuhan illustrated that at least 20% of patients who survived COVID-19 infection experienced encephalopathy.[19] A Chinese case report showed that about 20% of the patients that died from COVID infection, had findings in favor of encephalopathy.[20]

Another case report has been published that shows a possible correlation between COVID-19 infection and an acute hemorrhagic necrotizing encephalopathy in a 44-year-old woman that can be due to cytokine storm after COVID infection.[19] A possible way of predicting the virus complication is by comparing it to the HIV virus. HIV virus causes olfactory bulb damage and causes significant encephalopathy. In patients affected by HIV the reduced amount of olfactory function is correlated with their cognitive dysfunctions.[4,21,22] This matter may be also present in COVID-19 disease that needs further investigation. In patients with confessional state that were compatible with neuropsychiatric presentation of COVID-19, magnetic resonance imaging showed enhanced leptomeningeal and hyper perfusion in the area of frontal and temporal lobes.[12] Electroencephalogram evaluation did not show any specific pattern except diffuse slowing in the background that was compatible with encephalopathy.[12]

Anxiety

Simultaneous with COVID-19 pandemic, we have pandemic of fear of getting COVID-19 which is related to the abrupt change of people's life conditions.[23] The anxiety caused by fear of dying can impair the cognitive functions such as memory, attention, learning, decision making, similar to other stressors.[24,25] In a study conducted in the US and Canada, people who had previous anxiety disorders were more prone to the stress caused by COVID-19 pandemic.[26] The COVID-19 lockdown as well as the pandemic, increased depression and anxiety among individuals. In a study on 5545 random people in Spain, 65% reported depression and anxiety symptoms during the COVID-19 pandemic. They measured these symptoms by validated questionnaires (General anxiety disorder 7-item questionnaire, patient health questionnaire 9) (GAD-7, PHQ-9). After an intervention on their lifestyle including the prohibition of bad news and promoting their diet to a healthy and balanced one, they were able to significantly reduce depression and anxiety symptoms; however, it should be mentioned that the study was cross-sectional and did not show causality.[27]

In a study on 114 patients with positive COVID-19 test, PHQ-2 and GAD-2 questionnaires were used to assess depression and anxiety, respectively. Among COVID-19 presentations, only anosmia and agnosia were correlated with depression and anxiety symptoms. This matter

can be explained in two ways. Dysfunction in chemosensation had been shown to be correlated with anxiety, depression and less satisfaction of life. On the other hand, as COVID-19 can directly invade and damage the olfactory bulb, this positive correlation may prompt a hypothesis that depressed mood and anxiety may also be a result of direct invasion of the virus.[28]

Stroke

In a study on 174 patients with acute stroke and positive COVID-19 test, the National Institutes of Health Stroke Scale was 10 vs 6 in the control group, and their mortality rate and disability rate were 26.7% and 51%, respectively.[29] In another study**,** Cognitive function was examined in 227 patients three months after admission to hospital for ischemic stroke, and in 240 stroke-free controls, using 17 scored items that assessed memory, orientation, verbal skills, visuospatial ability, abstract reasoning, and attentional skills.[30] Cognitive impairment, defined as failure on any four or more items, occurred in 35.2% of patients with stroke and in 3.8% of the controls. Among patients with stroke, cognitive impairment was most frequently associated with major cortical syndromes and with infarctions in the left anterior and posterior cerebral artery territories.[30]

In a study on 645 subjects, 38% of patients had cognitive impairment in the three-month follow-up. Cognitive impairment was associated with age older than 75, left hemispheric strokes, visual field defects, and degree of disability.[31] In a study on 170 patients with stroke or transient ischemic attack, the cognitive dysfunction was associated with white matter lesions not the volume and number of lesions.[32] This matter should be considered in justifying stroke lesions in the patients with stoke and COVID-19. In a four-year follow-up study of patients with acute stroke, 84% of patients had severe cognitive dysfunction in favor of post-stroke dementia (Montreal Cognitive Assessment: 20±4.7). this indicates an important indication for cognitive assessment and rehabilitation for patients with acute stroke.[33]

Hypoxia

Another potential cause of cognitive dysfunction in patients affected by COVID-19 is hypoxia. We have inferred from previous research on sleep apnea that hypoxia induces cognitive impairments.[34] Since hypoxia can be related to and caused by acute respiratory distress syndrome (ARDS) or pulmonary embolism[35] in these patients, COVID-19 can cause hypoxia through various pathways. It can also suppress the central respiratory system in the medulla.[14] Interventions for improving hypoxia can be positioning the patients in the prone position and using thrombolysis with tissue plasminogen activator.[36] ARDS results in hypoxemia and uremia which leads to platelet dysfunction, epithelial damage, disseminated intravascular coagulation and presumed elevated risk of cerebrovascular accident.[37]

Cognitive Impairments in COVID-19

Sometimes, neurological symptoms can be a part of COVID-19 symptoms. In a study 36% of 39 patients had impairments in the executive function that can explain the prevalence of attention impairments and confusion in the reported articles which suggests a dysfunction in the frontal lobe area.[38,39] Elder patients, especially those with medical comorbidities, have a higher risk of developing psychiatric symptoms after COVID infection. They have even a higher risk of mood disturbance after recovering from the infection and hospital discharge. Some of them reported anxiety, depressed mood, post-traumatic stress disorder, and increased cognitive impairments. In a prospective study in the United Kingdom on 431 051 patients with different risk factors for getting COVID-19 infection, after controlling the social risk factor, only patients with higher cognitive impairments had higher risk of SARS-Cov-2 infection.[40] In the terms of classifying the domains of cognitive dysfunction, a retrospective study in the united states indicated that 24% of 50 patients had impairments in the short-term memory.[41] In a study on patients with acute and subacute COVID-19 infection that had neurological symptoms, the prevalence of neuroimaging characteristics were investigated. About a third of patients had diffuse hyper/hypo densities that were compatible with leukoaraiosis and leukoencephalopathy.[42]

As a result of quarantine, social isolation, impairs cognition through decreasing social interaction, cognitive training programs and results in increased feeling of loneliness that especially deteriorates the cognitive functions in the elderly with dementia.[43] In the elder patients hospitalized for COVID-19 infection, the most prevalent neurological syndrome was altered level of consciousness[44] and also they may present with some aberrant symptoms such as loss of appetite, confusional state, sudden onset of disorientation and psychological distress which may lead to denial of receiving proper treatment.[45] In a recent study conducted in Spain in 2020, among the patients with positive COVID-19 test, 10 patients had psychotic features with no previous history of psychiatric problem. Some of them even developed psychosis as auditory hallucination and delusion. In the psychological tests they had attention deficit but fortunately the symptoms resolved after 2 weeks of onset. These transient episodes of psychosis can be due to systemic inflammation and side effects of COVID-19 treatment as well as ICU care.[46] Cognitive impairment can also be a side effect of treatments for COVID-19, as shown in a study in four patients COVID-19 requiring ICU admission. The patients developed impairments in memory and functions of frontal lobe which exacerbated

with treatment with immunoglobulin after five days.[47]

Role of Inflammation in Cognitive impairment of COVID-19

Recently published studies have shown a systemic inflammation called "cytokine storm". As COVID-19 can cause pro-inflammatory cytokines release i.e. tumor necrosis factor and inteleukine-6, blood brain barrier will be disrupted and glial and neural cells of the brain can be damaged resulting in neurocognitive symptoms.[48,49]

There is also evidence of inflammation in neurodegenerative processes similar to Alzheimer's disease which shows the shared pathological mechanism in COVID-19 in which cognitive impairments are associated with neurodegenerative diseases.[50] In animal studies it is shown that the hippocampus is susceptible for viral infections resulting in memory deficit especially in the spatial memory domain.[51,52] Considering these studies, it is presumed that COVID-19 can cause cognitive impairments by inducing systemic inflammation.

Proposed Treatments of Cognitive Impairment in COVID-19

In the managing of patients with presumed cognitive dysfunction because of hypoxia, it is important to position the patient in the prone position and consider using thrombolysis if embolic source is suspected. In the patients with agitation that are cooperative in using pills, second generation of antipsychotics like aripiprazole, quetiapine and olanzapine is preferred. But in the patients that refuse to take medications, chlorpromazine can be effective. There is also a study that indicates a promising role of haloperidol by effecting the sigma receptor to treat SARS-CoV2.[53] Dexmedetomidine and clonidine patches can also be used to decrease anxiety in patients admitted to the ICU. Benzodiazepine are not usually preferred because of the increased risk of sedation and respiratory failure.[11] As we have significant cognitive impairments in patients infected by COVID-19, cognitive rehabilitation therapy has an important role to improve their function and escalate the independence.[54]

Cognitive rehabilitation therapy can also reduce the effect of cognitive impairments in the patient's daily life.[55] Recent studies showed that some computer-based cognitive rehabilitation programs in form of brain exercise games can have an improving effect.[56] The role of cognitive behavioral treatments in reducing the detrimental effect of anxiety should be considered.[57]

Conclusion

Among patients affected by COVID-19, there are different mechanisms that can cause cognitive dysfunction (Figure

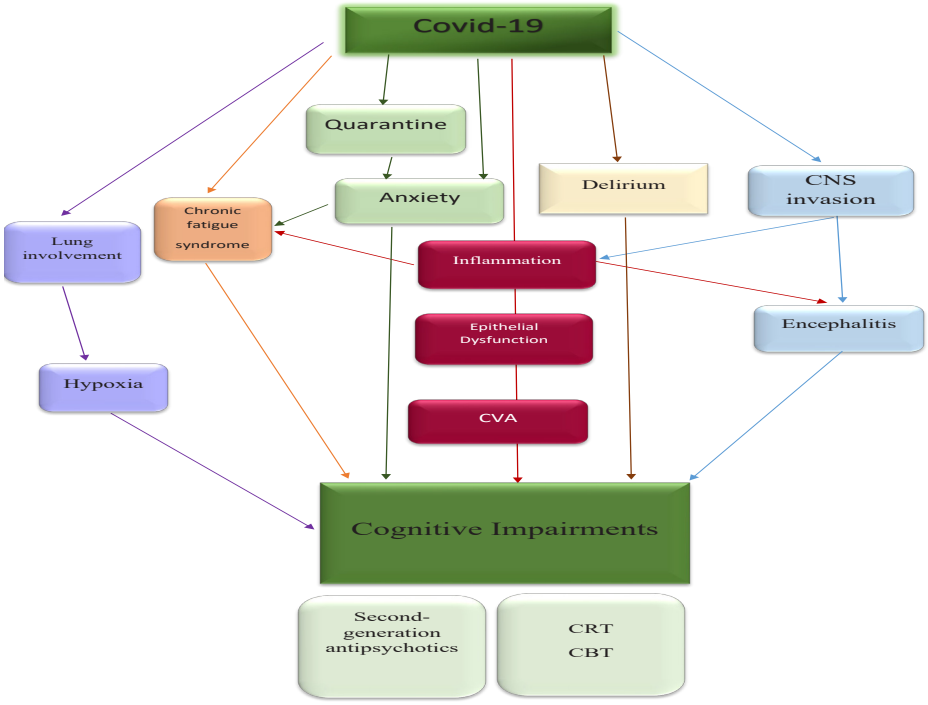

Figure 1. COVID -19 can cause direct invasion to CNS that causes inflammation and encephalitis. Inflammation can cause delirium, epithelial dysfunction and CVA and also causes chronic fatigue syndrome which is correlated with cognitive impairments. COVID-19 can require quarantine which increases anxiety that impairs cognition. COVID-19 also involves the lungs and induces hypoxia which deteriorates brain functions. The proposed treatments for cognitive impairment in the patients with COVID-19 infection, second generation antipsychotics, cognitive rehabilitation therapy and cognitive behavioral therapy is proposed.
CNS: Central nervous system, CVA: Cerebrovascular accident, CRT: Cognitive rehabilitation therapy, CBT: Cognitive behavioral therapy.

1). COVID-19 can affect the CNS directly by invasion and indirectly by inducing hypoxia, inflammation and delirium. The pandemic and fear of infection can also cause anxiety which impairs the cognition as well. By assessing the patients' cognition and knowing the higher probable cause of cognitive impairment, we can form a better strategy to better treat the impairment. Cognitive behavioral treatment can be effective in reducing the anxiety and cognitive rehabilitation therapy can be used to lower the detrimental effects of cognitive impairment caused by COVID-19.

Conflict of Interest

The authors declare that they have no conflict of interest. The authors have no financial support from any organization.

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Authors' Contribution

MaR and MeR gathered the information and wrote the original draft. HP supervised the research and reviewed the manuscript. AE , AS and SS edited the manuscript and designed the figure. MaR MeR and HP prepared the final manuscript. All authors contributed, reviewed and approved the final draft of the paper.

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Ethical Statement

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