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Evaluation of Postinfectious Neurocognitive Status in COVID-19 Patients

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Abstract

Objective: The coronavirus disease 2019 infection may have multisystemic manifestations including neurological involvement. The number of recognized neurologic manifestations of severe acute respiratory syndrome coronavirus 2 infection is rapidly accumulating, including neurocognitive decline. This study aimed to evaluate and monitor the temporal course of the neurocognitive status of patients who had been infected with the coronavirus disease 2019.

Methods: A total of 49 patients were included. Sex, demographics, and atherosclerotic risk factors were noted. The patients' global cognitive state performance was evaluated with Mini-Mental State Examination, Clock Drawing Test, Beck's Depression Inventory, and Barthel Activities of Daily Living index. The patients were evaluated 2 times within a 6-month interval.

Results: Of the patients, 53.1% were male, and the mean age was 43.3 ± 13.8 years. About 32.6% of the cases were found to have atherosclerotic risk factors at the first admission, and 34.7% of the patients needed to be hospitalized due to their symptoms. Mini-Mental State Examination score was found to be lower in patients with atherosclerotic risk factors ($P = .023$) and hospitalized patients compared to those in home quarantine ($P = .016$). In addition, lower points in Mini-Mental State Examination-1 scores were found in patients who needed to use steroids and tocilizumab (P values 0.029 and 0.022, respectively). Mini-Mental State Examination-1 and Mini-Mental State Examination-2 points of cumulative Mini-Mental State Examination change groups were significantly different ($P < .001$ and $P = .002$, respectively). In multiple comparisons, Mini-Mental State Examination-1 points of No change and Better were different ($P < .001$). Also Mini-Mental State Examination-2 points of No change and Worsened were different in multiple comparisons ($P = .002$).

Conclusion: Cognitive status should be closely monitored especially in elderly patients and patients with atherosclerotic risk factors.

Keywords: COVID-19 infection, cognitive impairment, dementia, brain fogging

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has spread rapidly worldwide since its first recorded case in the city of Wuhan, China, in December 2019. Although the symptoms are mainly related to the respiratory system, such as fever, cough, and shortness of breath, it is known that the virus not only affects the lungs but may also have multisystemic involvement, including the nervous system.

The most common neurological complication associated with COVID-19 infection was vascular disorders; other associated conditions were encephalopathy, facial nerve palsy, inflammatory demyelinating syndromes, Guillain–Barré syndrome, and so on.[1] A study in Wuhan, China, showed that 36.4% of the COVID-19 patients had neurological manifestations, mainly those patients with severe symptoms.[2] The etiology of neurological manifestations in COVID-19 may result from a variety of mechanisms, including virus-induced hyperinflammatory and hypercoagulable states, direct virus infection of the central nervous system (CNS), and postinfectious immune-mediated processes.[3] The mechanisms that lead to cognitive impairment associated with COVID-19 are not fully understood. Although the epidemiological and clinical features of COVID-19 patients are well characterized, the effect of the disease on cognitive functions has been demonstrated in limited studies. Few investigations have used objective neuropsychological measures to quantify cognitive deficits or characterize the extent and profile of cognitive dysfunction during recovery from COVID-19.

In a study, it is demonstrated that severely symptomatic COVID-19 patients who required hospitalization have impairments in many cognitive areas, especially memory, attention, and executive functions.[4] This "dysexecutive syndrome" is confirmed by other studies.[5,6]

In another study with COVID-19 patients who did not have dementia previously, moderate to severe cognitive impairment was found in 81% in the acute stages of the disease.[7] It is hypothesized that chronic hypoxia may cause cognitive deterioration by triggering both immune-mediated and degenerative processes.[8]

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In this study, we aim to determine the impact of cognitive functions, mood, and activities of daily living in COVID-19 patients. The second goal is to monitor and reveal the changes in the aforementioned parameters during the follow-up of the patients and thus disclose the effect of COVID-19 infection on neurocognitive status.

Material and Method

Patient Selection

Patients who were diagnosed with COVID-19 in our clinic between December 2020 and March 2021 and hospitalized or followed up in the outpatient clinic were included in the study. The first evaluation of the hospitalized patients was made when the disease activity was stabilized and discharge was planned. Patients who applied to the outpatient clinic within 1 month of the diagnosis of COVID-19 infection were also evaluated. The patients were telephoned and summoned to the outpatient clinic in the 6th month of their discharge and re-evaluated.

Patients who were 18 years of age or older and did not have a history of neurodegenerative disease were included in the study, and patients who could not cooperate in neurocognitive tests were not included. All the patients had a normal neurological examination during their visits. In the first evaluation, a total of 54 patients were tested, but since 5 patients could not be reached for the 6th-month controls, the total number of patients was determined as 49.

Neurocognitive Assessment

The patients' global cognitive performance was evaluated using the validated Turkish version of the Mini-Mental State Examination (MMSE).[9] Mini-Mental State Examination was performed interactively. After MMSE evaluation, Clock Drawing Test (CDT), Beck's Depression Inventory (BDI), and Barthel Activities of Daily Living (ADL) index were answered in the form of a questionnaire.

In CDT, the 4-point (0-4 points) method has been used because it is easier to establish with the patients in the form of a questionnaire. In BDI, we have categorized the patient results into 3 groups: minimal (0-9 points), mild (10-16 points), and moderate to severe (17 and more).

The patients were evaluated with the same method 6 months later at the outpatient clinic.

Statistical Analysis

Statistical Package for the Social Sciences version 21.0 (IBM SPSS Corp., Armonk, NY, USA) was used for the statistical analysis. Descriptive statistics were expressed as mean ± standard deviation for continuous and discrete numerical variables and in several cases as percentages (%) for nominal variables. The data expressed as percentages were compared using the Fisher–Freeman–Halto n test and the Chi-square test, while continuous variables were compared using the Mann–Whitney *U*-test. Values of $P < .05$ were considered statistically significant.

Ethical Approval

The Istanbul University-Cerrahpasa ethics committee (date: December 15, 2020, approval no: 160381) approved the study, and the necessary consent was obtained from the patients or the patients' relatives for their data to be used for scientific purposes.

Results

First Evaluation

A total of 49 patients were evaluated in which 26 were male (53.1%), and the mean age was 43.3 ± 13.8 years. Education level was below high school in 13 patients (26.5%), high school in 10 patients (20.4%), and above high school in 26 patients (53.1%). Sixteen patients (32.6%) were found to have atherosclerotic risk factors at the first admission. Seventy-five percent of patients with atherosclerotic risk factors were 50 years of age or older. Thirty-two patients (65.3%) had COVID-19 infection and were at home quarantine, 17 patients were needed to be hospitalized (34.7%) due to their symptoms, and only one of these patients required intensive care unit (ICU) admission. The complaint of brain fogging was experienced by 40 patients (81.6%) during the active infectious disease period.

The treatments during COVID-19 infection are summarized in Table 1. Almost all of the patients (93.8%) received antiviral treatment, 12 (24.4%) patients needed steroid treatment, and 8 (16.3%) needed tocilizumab treatment due to cytokine storm.

The MMSE values of the patients in the 1st month (MMSE-1) were observed in the range of 23-30 (mean value 28.2 ± 1.8). There was a weak negative correlation between age and MMSE-1 values ($r = –0.397$; $P = .005$). The MMSE-1 was found to be lower in patients with atherosclerotic risk factors compared to those without ($P = .023$). Regardless of age, no significant difference was found between MMSE-1 scores in patients with and without atherosclerotic risk factors (27.4 ± 1.9 and 28.6 ± 1.7; $P = .371$). The MMSE-1 was found to be lower in hospitalized patients compared to those in home quarantine ($P = .016$). In addition, lower MMSE-1 scores were found in patients who needed to use steroids and tocilizumab than in those who did not (*P* values 0.029 and 0.022, respectively). There was no significant difference between sex and education level in terms of MMSE-1 points. The patients' deficits in MMSE-1 were mostly observed in calculation and language (32.6%), followed by recall (30.4%). The least deficit was seen in attention (6.1%).

Thirty-two (65.3%) patients had a 4-point CDT-1 score. A moderate positive correlation was found between CDT-1 score and MMSE-1 score ($r = 0.466$; $P = .001$).

The BDI-1 scores were found in the range of 1-30 points (mean 9.4 ± 7.6). Twenty-eight (57.1%) patients had minimal, 13 (26.5%) patients mild, and 8 (16.3%) patients moderate to severe BDI-1 scores. There were no significant differences in sex, education level, hospitalization, and medication in terms of BDI-1 points.

Four (8.16%) patients had low ADL-1 scores; 75% of the patients were male, and the mean age was 65.5 ± 7.3 years. The ADL-1 was found to be lower in patients with atherosclerotic risk factors compared to those without ($P = .036$). It was found to be

Table 1. Summary of Medications Used in Covid-19 Patients

Treatments	Total Number (%)
No treatment	0
Plaquenil	5 (10.2)
Favipiravir	46 (93.8)
Steroids (oral and/or intravenous)	12 (24.4)
Tocilizumab	8 (16.3)
Acetylsalicylic acid (ASA)	22 (44.9)
Low-molecular-weight heparin (LMWH)	19 (38.7)
Anakinra	1 (2.04)
Vitamin D derivatives	14 (28.5)

lower in hospitalized patients compared to those in home quarantine (P = .05). In addition, lower ADL-1 scores were found in patients who needed to use steroids than in those who did not (P < .001). There were no significant differences between sex and education level in terms of ADL-1 points. A weak positive correlation was found between ADL-1 scores and MMSE-1 scores (r = 0.346; P = .015).

Second Evaluation

The MMSE values of the patients in the 6th month (MMSE-2) were observed in the range of 25-30 (mean value 28.7 ± 1.5). A medium negative correlation was found between age and MMSE-2 values (r = –0.478; P = .001). The MMSE-2 was found to be lower in patients with atherosclerotic risk factors compared to those without (P = .005). Regardless of age, MMSE-2 scores were found to be significantly lower in patients with atherosclerotic risk factors (27.7 ± 1.7; 29.1 ± 1.2; P = .046). The MMSE-2 was found to be lower in hospitalized patients compared to those in home quarantine (P = .028). There was no significant difference between sex, education level, or medication during the infection in terms of MMSE-2 points. The patients' deficits in MMSE-2 were mostly observed in the calculation (28.5%), followed by language (20.4%) The least deficit was seen in attention (2.04%).

Compared to the MMSE-1 evaluation, there were 7 (14.3%) patients with worsening in MMSE-2 points, 24 (49.0%) patients without change, and 18 (36.7%) patients with improvement in MMSE-2 points. The scores of MMSE and BDI according to cumulative MMSE change were summarized in Table 2. The MMSE-1 and MMSE-2 points of cumulative MMSE change groups were significantly different (P < .001 and P = .002, respectively). In multiple comparisons, MMSE-1 points of No change and Better were different (P < .001). Also MMSE-2 points of No change and Worsened were different in multiple comparisons (P = .002). No difference was found in BDI-1 and BDI-2 points of cumulative MMSE change groups (P > .05).

Thirty-six patients (73.4%) had a 4-point CDT-2 score. A weak positive correlation was found between CDT-2 score and MMSE-2 scores (r = 0.324; P = .023), and a moderate correlation was found between CDT-2 score and MMSE-1 scores (r = 0.459; P = .001).

The BDI-2 tests were found in the range of 1-31 points (mean value 10.3 ± 7.6). Twenty-six (53%) patients had minimal, 15 (30.6%) patients mild, and 8 (16.3%) patients moderate to severe BDI-2 scores). The BDI-2 was found to be lower in patients with atherosclerotic risk factors compared to those without (P = .018). Compared to the BDI-1 evaluation, there were 15 (30.6%) patients with worsening in BDI-2 points, 14 (28.5%) patients without change, and 20 (40.8%) patients with improvement in BDI-2 points. No difference was found in the BDI-1 and BDI-2 points of cumulative MMSE change groups (P > .05).

Barthel Activities of Daily Living-2 was found to be improved in 75% of patients with a low ADL-1 index.

All neurocognitive test scores are summarized in Table 3.

Table 2. Summary of Cumulative MMSE Changes and Its Relations with MMSE and BDI Scores

	Cumulative MMSE Changes			
	No Change (n = 24)	Worsened (n = 7)	Better (n = 18)	*P*
Age (mean ± SD)	40.4 ± 14.3	49 ± 9.5	45 ± 14.2	.106
MMSE-1 (mean ± SD)	29.2 ± 1.31	28.2 ± 1.49	26.9 ± 1.83	<.001[a]
MMSE-2 (mean ± SD)	29.2 ± 1.33	27.1 ± 1.34	28.6 ± 1.28	.002[b]
BDI-1 (mean ± SD)	9.9 ± 8.21	8.4 ± 7.63	9 ± 7.17	.870
BDI-2 (mean ± SD)	9.25 ± 7.02	15.1 ± 11.6	9.7 ± 6.02	.475

[a] MMSE-1 points of no change and better are different; [b] MMSE-2 points of no change and worsened are different.
ADL, Barthel Activities of Daily Living index; BDI, Beck's Depression Inventory; CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; SD, standard deviation.

Table 3. Summary of Evaluated Neurocognitive Test Scores

Test Name	Score Range (Mean ± SD)
MMSE-1	23-30 (28.2 ± 1.84)
CDT-1	0-4 (3.34 ± 1.36)
BDI-1	0-30 (9.3 ± 7.62)
ADL-1	85-100 (99.2 ± 2.7)
MMSE-2	25-30 (28.7 ± 1.46)
CDT-2	0-4 (3.53 ± 0.91)
BDI-2	0-31 (10.2 ± 7.58)
ADL-2	95-100 (99.8 ± 0.71)

ADL, Barthel Activities of Daily Living index; BDI, Beck's Depression Inventory; CDT, Clock Drawing Test; MMSE, Mini-Mental State Examination; SD, standard deviation.

Discussion

To our knowledge, this is the first study that performed 2 cognitive assessments within 6-month intervals in patients with COVID-19 infection. Neuropsychological assessment was performed in the early period after hospitalization to have the most recent possible cognitive profile related to the infection and its temporal relationship with the outcome. Although we were not able to administer a comprehensive neuropsychological evaluation in the inpatient setting, we demonstrated the outcome of the neurocognitive status of the patients within 6 months.

Few studies in the literature evaluated the follow-up cognitive status of COVID-19 patients. In one study, patients were called to the outpatient clinic 4 months after COVID-19 infection, and their cognitive symptoms were evaluated through a questionnaire. Cognitive symptoms were found in 38.4% of these patients, and it is observed that the majority of the patients were older than 75 years.[10] In another study, the cognitive status of patients was evaluated in the 4th month after ICU hospitalization due to severe COVID-19 infection. Among those patients, cognitive disturbance was found to be higher in patients with a history of delirium, need for mechanical ventilation during hospitalization, and higher serum inflammation markers.[11] In a study conducted with healthcare workers with mild-to-moderate COVID-19 infection and a healthy control group, patients were re-evaluated after 4 months of infection with MMSE. The study found that there is no significant

difference between the MMSE scores of patients with and without COVID-19.[12]

In our study, we found that there was a negative correlation between the age of the patients and their MMSE, CDT, and ADL scores. We also found a positive correlation between education level and CDT and MMSE scores in agreement with the literature.

Patients with moderate-severe BDI-1 scores persisted as moderate-severe in the second evaluation, and there was no correlation between BDI and MMSE scores. A study with COVID-19 patients showed that about 1 month after infection, depressive symptoms were seen in 31%-38% of patients, and anxiety symptoms were reported in 22%-42%.[13]

The scores of MMSE were found to be lower in patients with atherosclerotic risk factors. The MMSE-2 values were found to be lower in patients with atherosclerosis regardless of age. The MMSE and ADL scores were found to be lower in hospitalized patients, especially in those who received steroid treatment. It is correlated in a study performed with 54 patients, and it is found that individuals recovered from COVID-19 might show long-term memory deficits of diverse etiology, especially those having suffered from mid-to-moderate COVID-19 and those already at risk for cognitive decline.[14] In another study, it is hypothesized that cytokine storm in COVID-19 infection may cause cognitive impairment.[15] It was reported in previous studies that a history of dementia is associated with severe COVID-19 infection and an increased risk of hospitalization.[16] Although hospitalized cognitively impaired patients have higher mortality and morbidity rates, the presence of dementia alone is not an independent risk factor for mortality.[17] Despite this information, COVID-19 infection may also impair cognitive functions in healthy individuals.[7,18] Another study showed that the hospitalization rates of patients diagnosed with dementia before COVID-19 infection were similar to those of cognitively healthy individuals.[19]

The underlying etiology of the neurological manifestations of COVID-19 is not fully understood. Direct effects of the virus, postinfectious immune response, and microvascular damage due to hypercoagulability have been implicated. A study suggested that neurological manifestations of COVID-19 can be divided into indirect and direct effects of the virus.[20] Microvascular damage due to hypoxia and hypercoagulability has been suggested as the indirect effect of COVID-19. The direct effect of the virus is that it triggers the immune response causing demyelination, axonal damage, and encephalitis.[20] However, to what extent should COVID-19 be blamed for the complications caused by its indirect effect is not known. The critical illness itself can also lead to vascular complications with similar mechanisms. The pathological cascade that leads to neurodegeneration is not yet clearly elucidated. An aforementioned study hypothesized that chronic hypoxia may cause cognitive deterioration by triggering both immune-mediated and degenerative processes.[8] Chronic hypoxia due to long ICU admissions and critical illness may cause memory loss itself. It is found that hippocampus neurons are susceptible to hypoxic damage.[21] Various studies have been conducted to determine the extent of COVID-19 virus load in the CNS, and conflicting results have been obtained. In the postmortem examination of 27 cases, the COVID-19 virus has been isolated in a low titer in the CNS,[22] but in another study, CNS involvement could not be detected in the autopsy material of 10 patients.[23]

Although the etiology has not been fully elucidated, we found lower MMSE scores in elderly patients and patients with atherosclerotic risk factors. Considering that 75% of the patients with atherosclerotic risk factors are 50 years or older, we found that MMSE-1 scores were similar in patients with and without atherosclerotic risk factors, while MMSE-2 scores were found to be lower in patients with atherosclerotic risk factors independently of age. Therefore, we can speculate that patients with atherosclerotic risk factors are more susceptible to neurodegenerative processes after COVID-19 infection than patients without risk factors. Particular attention should be paid to secondary protection after COVID-19 infection, especially in elderly patients and patients with atherosclerotic risk factors.

The study was cross-sectional, and although none of these patients had documented history of neurodegenerative disorders, we do not know the patients' qualitative premorbid neurocognitive status. In the first wave of COVID-19 infection, we could not perform cranial MRI on our patients in the first wave of the pandemic. Another limitation is the lack of a control group to which to compare our patient group. Future studies should include advanced neuroimaging and a long-term follow-up assessment of the deficits to determine whether this could precipitate the onset of neurocognitive disorders.

Coronavirus disease 2019 infection may cause neurocognitive deterioration. Although the underlying etiology is not fully understood, it is hypothesized to be multifactorial. Virus-induced hyper-inflammation and post-viral immune dysfunction may be the key features of neurocognitive decline. Cognitive status should be closely monitored especially in elderly patients and patients with atherosclerotic risk factors. Clinicians and caregivers should consider the identification and assessment of these patients and a long-term follow-up to prevent further impairment. Further multicenter randomized controlled studies correlated with immune biomarkers and neuroimaging are needed to seek a possible association between COVID-19 and neurocognitive impairment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (date: December 15, 2020, Approval No: 160381).

Informed Consent: Written informed consent was obtained from patients or the patients' relatives who participated in this study.

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