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Evaluation of cognitive deficits in patients infected with COVID-19

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Abstract. – OBJECTIVE: COVID-19 infection can cause impairments in many cognitive areas. The aim of the present study was to evaluate the cognitive functions of patients who had been infected with COVID-19.

PATIENTS AND METHODS: The demographic and infection-related characteristics of patients who had been infected with COVID-19 were determined. Their cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) findings were recorded. The Mini-Mental State Evaluation (MMSE), clock drawing test, forward and backward digit span tests, visual memory test, and Frontal Assessment Battery were applied to the patients. Finger agnosia and ideomotor apraxia were also determined.

RESULTS: The study included 176 patients [100 female (56.8%), 76 male (43.2%), mean age 66.09±13.96 years]. About half of the patients were hospitalized for symptoms of COVID-19 infection (n=82, 46.6%). One third of these patients required intensive care (n=26, 14.8%). While 50 (45.9%) of the 109 patients diagnosed with dementia before infection were hospitalized, 32 (47.8%) of the 67 patients without a diagnosis of dementia required hospitalization (p=0.46). The most common neurological finding during COVID-19 infection was insomnia (n=36, 20.5%). The MMSE and visual memory test scores of the patients who were hospitalized for severe respiratory distress were lower than those whose treatment at home was completed (respectively 17.92±7.69/20.59±7.01, p=0.02; 2.53 ±1.73/3.69±2.80, p=0.01). The patients with moderate to severe cognitive impairment had significantly higher CRP levels at admission than the others (37.52±43.09/20.93±31.74, p=0.01, respectively).

CONCLUSIONS: Cognitive damage in COVID-19 infection may be caused by ACE receptor density in the pial, hippocampal, and amygdala areas. In addition, the reason why people with severe dementia have a milder infection might be explained by the atrophy in these areas.

Key Words:
COVID-19 infection, Cognitive deficits, Alzheimer's disease, Dementia.

Introduction

Coronavirus (COVID-19) infection can affect the central nervous system, as well as the respiratory tract, and cause neurological symptoms. During the illness, symptoms including dizziness, sleep disturbances, cognitive impairment, delirium, and hallucinations are observed[1]. In addition, it has been reported that severely symptomatic people who have this infection, especially those who require hospitalization, have impairments in many cognitive areas, especially memory, attention, and executive functions[2,3]. In a study[4] conducted with people who did not have dementia previously, moderate to severe cognitive impairment was found in 81% in the early stages of the disease. In another study[5] evaluating the 3-month follow-up of patients infected with COVID-19, 78% of the patients showed poor performance in at least one cognitive area and this was predicted based on the immune inflammation levels at the beginning of the disease.

The systemic inflammation caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease, dis-

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rupts the blood-brain barrier, causing GABAergic damage and neuronal degeneration in the brain[6]. Therefore, the hypoxic process that develops due to pneumonia can also affect the brain and increase oxidative neuronal damage and inflammation[7]. The expected increased risk of thrombosis and stroke during the course of the disease also contributes to the development of cognitive damage[8]. In a limited number of studies, it has been suggested that experimentally induced cerebral hypoperfusion increases amyloid β deposition and triggers tau and TDP-43 pathology[8]. In another study[9], it was reported that olfactory dysfunction, which may occur in COVID-19 patients with a homozygous mutation of ApoE e4, may trigger the development of dementia. All these indicate that COVID-19 infection can significantly increase the incidence of neurodegenerative disorders and cause neuronal damage triggering dementia.

Although it is not clear which cognitive functions are affected by COVID-19 infection and to what extent, it is thought that the disease increases decline in cognitive function[6]. However, studies[3-5] in which cognitive functions are evaluated using objective neuropsychological tests during the subacute and/or chronic periods in people with this infection are limited to patient series or studies with small samples.

In the present study our aim was to determine in which areas and how severely the cognitive functions of patients with COVID-19 infection may be impaired. Another aim was to reveal patient and disease characteristics that may be associated with cognitive damage.

Patients and Methods

Patients

This cross-sectional observational study included 176 patients (100 female, 76 male) who presented to the neurology outpatient clinic of four different university hospitals and were found from their anamnesis and medical records to have been infected with COVID-19 and to have completed their treatment. The patients underwent detailed neurological and cognitive examinations performed by neurologists. Their age, sex, marital status, education and employment status, tobacco and/or alcohol use, systemic and neurological diseases, and family history of dementia were recorded. In addition, in order to determine the severity of the COVID-19 infection suffered by the patients, they were asked about the presence of hyposmia and/or anosmia symptoms during this infection, respiratory distress and the need for oxygen therapy, ward and/or intensive care unit hospitalization, epileptic seizure history, and how many days after infection they were evaluated. Serum C-reactive protein (CRP), ferritin, D-dimer, and lymphocyte levels at diagnosis were measured to evaluate the relationship between the severity of infection and the cognitive status of the patients. The reference values used were a CRP level below 1.0 mg/L, serum ferritin level above 50 mL/ng, D-dimer level below 500 μg/L, and serum lymphocyte level between 1000 and 4800 μL.

The cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) findings of the patients, if available, were recorded.

Patients with vision and hearing problems that would prevent the application of neuropsychological tests and those with severe systemic diseases that could affect cognitive status were excluded from the study.

Ethics Committee approval was obtained for the study (Gülhane Training and Research Hospital Scientific Research Ethics Committee, Project/Decision No: 2021-110, Date: March 11, 2021) and the necessary consents were obtained from the patients' relatives for their data to be used for scientific purposes. The study was conducted in accordance with the principles of the 2008 Declaration of Helsinki.

Neuropsychological Evaluation

The neuropsychological tests were performed by neurologists specialized in this field. The patients' global cognitive performance was evaluated using the Turkish version of the Mini-Mental State Examination (MMSE)[10]. Additional detailed neuropsychological tests were applied to evaluate the following areas: (1) Visuospatial functions, sequencing, planning, and abstract thinking (clock drawing test)[11], (2) Attention (forward and backward digit span tests[12], (3) Construction ability and visual memory (visual memory test), (4) Frontal lobe functions such as conceptualization, mental flexibility, motor programming, and inhibitory control (Frontal Assessment Battery)[13]. The patients were also examined for the presence of finger agnosia and ideomotor apraxia.

The four-point (0-4 points) method was used because it is easier when scoring the clock drawing test (CDT). In the four-point method, 1 point is given for a closed circle (outside of the clock), for numbers of the clock in the right place and po-

sition, for all 12 numbers (complete), and for the hour and minute hands in a position to show 11:10 correctly. The highest score that can be obtained from this version of the CDT is 4 and the lowest score is 0. In the digit span tests applied to evaluate simple attention, random 2- to 8-digit number sequences were given for the forward digit span and random 2- to 7-digit number sequences for the backward digit span. One point was given for each item counted correctly. In the visual memory test, patients were given four shapes (circle, rhombus, two interlocking rectangles, and cube) and told to copy these shapes. Approximately 15 minutes later, the patients were asked to redraw these previously shown figures as well as they could remember. Each correct operation was scored with one point and the highest score that could be obtained from this test was 11. The Frontal Assessment Battery was applied. It consisted of six subsections assessing conceptualization, mental flexibility, programming, sensitivity to interference, inhibitory control, and environmental autonomy and was scored between 0 and 18 points. For the finger agnosia test, the patients were asked to indicate which finger they were being shown of five different fingers shown one by one from the right and/or left hand. The finger numbers they gave correctly were recorded.

Statistical Analysis

SPSS 21.0 (Statistical Package for the Social Sciences, IBM, Armonk, NY, USA) was used for the statistical analysis. Descriptive statistics were expressed as mean ± standard deviation for continuous and discrete numerical variables, and as number of cases and percentages (%) for nominal variables. The data expressed as percentages were compared using the Fisher-Freeman-Halton test and chi-square test, while continuous variables were compared using the Mann-Whitney U test. Values of $p< 0.05$ were considered statistically significant.

Results

This study included 176 patients [100 female (56.8%), 76 male (43.2%), mean age 66.09±13.96 years] who had been infected with COVID-19. Some 71% (n=125) of the patients were married. Most of them were retired or not working (n=135, 76.7%) and 141 (80.1%) of the patients had a history of systemic diseases such as hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, thyroid dysfunction, and rheumatologic disease. In addition, 147 patients (83.5%) had a neurological disease diagnosed before COVID-19 infection. Of these, 109 had a diagnosis of dementia. Only 69 patients (39.2%) had a family history of dementia. Cranial MRI was performed in 161 (90.5%) of the patients. In neuroimaging, the most common lesions were multiple ischemic gliotic lesions (40.3%) and bilateral temporoparietal or frontotemporal atrophy (14.8%). While 18.6% (n=33) of the 174 patients in which EEG had been performed were normal, generalized slow delta/theta activity was observed in 29.4% (n=52) (Table I). About half of the patients were hospitalized for symptoms of COVID-19 infection (n=82, 46.6%). One third of these patients required intensive care (n=26, 14.8%). Of the 72 patients who had respiratory distress at the time of infection, 68 received oxygen therapy with intranasal or noninvasive mechanical ventilation. Almost all of them completed antiviral treatment (favipiravir 1200 mg/day/5-10 days) (n=171, 97.2%). While 43 (24.4%) of the patients described hyposmia/anosmia, 9.1% (n=16) stated that they had epileptic seizures while infected with COVID-19. The most common neurological finding during COVID-19 infection was insomnia (n=36, 20.5%). This was followed by delirium, with 19.3% (n=34), and hallucinations, with 14.2% (n=25). The other neurological findings observed are summarized in Table I. The patients were evaluated by neuropsychological tests 37.56±33.27 days on average after the diagnosis of COVID-19 infection. The neuropsychological test scores of the patients are summarized in Table II. Those with systemic disease and those with respiratory distress needing oxygen required more hospitalization than those without (p=0.008, p=0.001, p=0.001, respectively). While 50 (45.9%) of the 109 patients diagnosed with dementia before infection were hospitalized, 32 (47.8%) of the 67 patients without a diagnosis of dementia required hospitalization (p=0.46). The MMSE and visual memory test scores of the patients who were hospitalized for severe respiratory distress were lower than those of the patients whose treatment was completed at home (respectively 17.92±7.69/20.59±7.01, p=0.02; 2.53±1.73/3.69±2.80, p=0.01). The neuropsychological test scores of the patients who were hospitalized and of those whose treatment was completed at home are given in Table III. The patients with moderate to severe cognitive impairment had significantly higher CRP levels

Table I. The patients' demographic and clinical characteristics.

	N (%)
Sex, Female	100 (56.8)
Marital status	
Married	125 (71)
Widowed/divorced	44 (25)
Single	7 (4)
Employment status	
Retired/works at home	135 (76.7)
Full-time employee	35 (19.9)
Part-time employee	6 (3.4)
Presence of systemic disease	141 (80.1)
Presence of neurological disease	
None	29 (16.5)
Vascular dementia	35 (19.9)
Alzheimer's disease	34 (19.3)
Dementia with Lewy bodies	14 (8)
Past stroke	13 (7.4)
Parkinson's disease	12 (6.8)
Frontotemporal lobar degeneration	10 (5.7)
Other (hydrocephalus, carotid stenosis, epilepsy, venous thrombosis, migraine, polyneuropathy, motor neuron disease, essential tremor, myasthenia gravis, multiple sclerosis)	29 (16.4)
Tobacco use	64 (36.4)
Alcohol use	9 (5.1)
Presence of dementia in the family	69 (39.2)
Neurological findings seen during COVID-19	
Insomnia	36 (20.5)
Delirium	34 (19.3)
Hallucinations	25 (14.2)
Headache	22 (12.5)
Increased forgetfulness	16 (9.1)
Tremors	9 (5.1)
Perceptual impairment	6 (3.4)
Hemiparesis	6 (3.4)
Dizziness	4 (2.3)
Apathy, confusion, encephalopathy	4 (2.3)
Epileptic seizures	4 (2.3)
Ptosis	1 (0.6)
Cranial MRI	
Normal	16 (9.1)
Multiple ischemic gliotic foci	71 (40.3)
Temporal/frontotemporal atrophy	26 (14.8)
Widespread atrophy	12 (6.8)
Infarcts	7 (4)
Other	37 (25)
EEG	
Normal	33 (18.6)
Generalized slow delta/theta activity	52 (29.4)
Bilateral frontotemporal theta activity	41 (23.2)
Bilateral frontoparietal central theta activity	23 (13)
Slow waves, sharp slow waves, ictal activity etc. in other locations	25 (15.8)

at admission than those with normal or mild cognitive impairment (37.52±43.09/20.93±31.74, $p=0.01$, respectively).

Serum ferritin, D-dimer, and lymphocyte levels at the time of diagnosis were similar between the groups (p=0.41, p=0.28, p=0.87).

Discussion

Our study shows that the cognitive functions of people infected with COVID-19 were adversely affected after about 1 month, and the cognitive performance of those with severe infection re-

Table II. Neuropsychological test scores after COVID-19 infection.

	Mean ± SD (N)
Mini-Mental State Examination	19.39 ± .42 (169)
Clock drawing test	2.56 ± 1.45 (156)
Frontal Assessment Battery	11.11 ± 4.21 (126)
Forward digit span	4.01 ± 1.46 (130)
Backward digit span	2.51 ± 1.69 (130)
Visual memory test	3.16 ± 2.43 (138)
Finger agnosia test	3.05 ± 1.65 (176)

SD: standard deviation, N: number.

quiring hospitalization was worse than that of those not requiring hospitalization. Furthermore, those with moderate to severe cognitive impairment had higher initial CRP levels. It was also determined that patients with a previous diagnosis of dementia had milder COVID-19 infection and outpatient treatment was sufficient.

COVID-19 infection is thought to impair cognitive functions in healthy individuals. It has been shown in previous studies[4,5] that 78-81% of healthy individuals who were previously found to be cognitively sound had difficulties in at least one cognitive area according to their post-infection assessments. The areas affected most are executive functions, attention, psychomotor coordination, information processing, verbal fluency, and working memory[4,5]. In addition, approximately one third of those with this infection had dysexecutive syndrome, and confusion and attention disorders predominated in these patients[2,14]. It is known that sustained attention and executive functions in particular are more affected than memory[6]. In contrast, it has been reported that 24% of elderly COVID-19 patients treated in hospital had recent memory impairment[15]. Attention, orientation, and memory disorders may continue after discharge in the elderly with serious infection requiring intensive care[14,16]. In agreement with the literature, global cognitive functions, especially memory, attention, and executive functions, were negatively affected in the patients in our study. Moreover, global cognitive functions and visual memory in the patients who were hospitalized for treatment were worse than in those whose outpatient treatment was completed. In the inpatient group, attention was relatively preserved and the worsening of memory performance may have been due to the fact that more than half of our patients had a history of dementia diagnosed before infection.

It is known that the need for follow-up in the intensive care unit and the application of invasive treatments such as ventilation and/or sedation after acute respiratory distress syndrome (ARDS) are risk factors for cognitive decline[17]. Similarly, neurological findings during COVID-19 infection, diarrhea, and the need for oxygen therapy due to clinical hypoxia are also risk factors for neurocognitive impairment compared to asymptomatic individuals[3]. In our study, similar to the results of previous studies, the patients with hypoxia and needing respiratory support were hospitalized more frequently and the cognitive functions of hospitalized patients were worse.

In previous studies[18,19] it was reported that a history of dementia is associated with severe COVID-19 infection and that patients with Alzheimer's disease (AD) and/or Parkinson's dementia with this infection have an increased risk of hospitalization. Although hospitalized dementia patients have higher mortality and morbidity rates, the presence of dementia alone is not an independent risk factor for mortality[20]. It is thought that factors such as fewer core symptoms of COVID-19 infection such as cough in people with dementia, delayed access to treatment and hospital standards due to patients' atypical symptoms, advanced age (over 80 years old), comorbid diseases, and residence in nursing homes play a

Table III. Location of the brain lesions at conventional MRI performed after 3 months of stroke.

	Hospitalized patients mean ± SD (N)	Outpatients mean ± SD (N)	*p*
MMSE	17.92 ± 7.69 (76)	20.59 ± 7.01 (93)	0.02*
Clock drawing test	2.35 ± 1.60 (68)	2.75 ± 1.31 (88)	0.09
Frontal Assessment Battery	10.94 ± 4.28 (52)	11.22 ± 4.1 (74)	0.70
Forward digit span	3.92 ± 1.58 (63)	4.10 ± 1.33(67)	0.47
Backward digit span	2.71 ± 1.79 (63)	2.32 ± 1.58 (67)	0.19
Visual memory test	2.53 ± 1.73 (63)	3.69 ± 2.80 (75)	0.01*
Finger agnosia test	2.85 ± 1.73 (82)	3.22 ± 1.56 (94)	0.13

SD: standard deviation, N: number, MMSE: mini-mental state examination, *p-value < 0.05.

role in morbidity[21,22]. In a study involving a large cohort of 6364 people[23] it was found that pre-existing cognitive damage did not pose a higher risk for COVID-19 mortality. Our findings showed that the hospitalization rates of patients diagnosed with dementia prior to COVID-19 infection were similar to those of cognitively healthy individuals. This finding conflicts with the idea that the presence of dementia will increase hospitalization. This can be explained by the fact that patients with dementia have easy access to diagnostic tests in this country, they are diagnosed quickly, antiviral and supportive treatment is started immediately, and the infection is controlled at the beginning and appropriately.

Recent research[24] has shown that angiotensin-converting enzyme 2 (ACE-2) acts as a receptor for COVID-19. On the other hand, it has been suggested that ACE-2 is one of the main enzymes that releases neurotrophic factors regulating normal cognitive functions through some important proteins such as Mas protein. Moreover, a strong correlation was found between decreased ACE-2/angiotensin (AT) (1–7)/Mas axis activity and tau hyperphosphorylation and amyloid-β (Aβ) aggregation[25]. These findings suggest that the decrease in ACE-2 activation may impair normal cognitive functions or increase the risk of AD. Furthermore, the relationship of AT-III with amyloid β and tau pathology is known[26]. In AD, it has been shown that ACE-2 protein levels are downregulated in the basal ganglia, hippocampus, entorhinal cortex, middle frontal gyrus, visual cortex, and amygdala[27]. The presence of APOEe4 has also been hypothesized to be associated with severe COVID-19 infection in patients with dementia[28]. The milder incidence of this infection in people with severe dementia in our study can be explained by atrophy of the mentioned areas. However, this hypothesis could not be confirmed in the present study because the APOE4 positivity of our patients was not known. In addition, to the best of our knowledge, there is no study showing the effect of COVID-19 infection on cognitive deterioration in patients with dementia. There is a need for randomized controlled prospective studies to examine whether people with severe dementia will have a milder COVID-19 infection due to the atrophy in the regions in which ACE2 receptor density is high.

In COVID-19 patients, proinflammatory cytokines such as TNFα, INFγ, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, MCSF, and HGF and chemokines such as CXCL8, MCP1, IP10, MIP1α, and MIP1β are found at high levels[29]. The same proinflammatory cytokines and chemokines are also frequently increased in the brains of AD patients[30,31]. The cytokine storm and associated severe respiratory distress, coagulation problems, multiorgan failure, cardiovascular abnormalities, impaired immune response, neurovascular complications, and neuroinflammation in COVID-19 patients can cause cognitive impairment[32,33]. In particular, impairment of sustained attention is associated with inflammatory processes measured by CRP[6]. Therefore, it has been suggested that interferon suppression may be a treatment strategy that can be applied to control the increased immune response in AD and COVID-19 infection, and that cholinergic anti-inflammatory pathway stimulation may be beneficial for controlling the cognitive damage that develops after this infection[31]. Similarly, our results revealed that patients with moderate to severe cognitive impairment had higher CRP levels at the time of diagnosis.

SARS-CoV-2 may affect the frontal lobes of the brain, causing dyssexual and behavioral symptoms in patients with COVID-19 infection. Frontotemporal hypoperfusion and hypometabolism were detected in the brain MRI and 18F-FDG-PET imaging of these patients, and slowing was demonstrated in the frontal regions in their EEGs[22]. In the present study, temporal/frontotemporal atrophy and multiple ischemic gliotic foci were observed in more than half of the patients. However, no further studies were conducted to evaluate the relationship of these findings with existing cognitive functions. In approximately half of our patients, generalized or bilateral frontotemporal slow wave activity was observed on EEG, which is consistent with previous studies.

Most of the patients included in our study stated that they had had at least one neurological complaint while infected with COVID-19. The most common neurological findings were insomnia, delirium, hallucinations, and headache. These findings are similar to those reported in previous studies. Neurological symptoms are quite commonly observed in older patients with this infection[34,35]. The most common neurological findings are sleep disturbances, confusion, headache, dysgeusia, anosmia, myalgia, dizziness, and encephalopathy[3,18,36]. Confusion, delirium, and encephalopathy are the most common findings observed in patients with dementia[20,37,38].

Although the present study included a large sample in which the cognitive functions of patients with COVID-19 infection in the subacute period were evaluated in detail with standardized neuropsychological tests and supported by laboratory results and brain MRI and EEG findings, the study had some limitations. The study was cross-sectional and post-infection cognitive progression in the dementia patients could not be determined. The lack of a control group was another limitation.

Conclusions

Infection with COVID-19 may increase the frequency of future neurodegenerative disease. Cognitively intact individuals with this infection should be followed up in this context, in particular because of the intensity of ACE-2 receptor expression in the pial, hippocampal, and amygdala regions. Furthermore, it is important to follow up these patients and develop appropriate treatment strategies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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