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COVID-19 Associated Brain Fog and Neurocognitive Assessment

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Abstract

BACKGROUND/AIMS: In this study, we aimed to make detailed neurocognitive assessments of patients who presented with brain fog after coronavirus disease-2019 (COVID-19) infection and to investigate their complaints after one-year of follow-up.

MATERIALS AND METHODS: Patients who had COVID-19, which was not severe enough to require intensive care, and who subsequently applied to neurology due to cognitive complaints were included in this study. A neurocognitive test battery was applied to those patients who agreed to detailed examination (n=16). This battery consisted of the following tests: mini-mental test, enhanced cued recall test, phonemic fluency, categorical fluency, digit span, counting the months backwards, clock-drawing, arithmetic operations, trail-making, cube copying, intersecting pentagons, and the interpretation of proverbs and similes. At one year, the patients were called by phone and questioned as to whether their cognitive complaints had persisted. Those patients with ongoing complaints were invited to the hospital and re-evaluated via cognitive tests. The results are presented in comparison with age-matched healthy controls (n=15).

RESULTS: Almost all of the patients' scores were within the "*normal*" range. The *Spontaneous recall* of the patients was statistically significantly lower than the controls (p=0.03). Although there were decreases in executive functions and central processing speed (trail making-A, trail making-B and reciting the months backwards tests) in the patient group, these differences were not statistically significant (p=0.07; p=0.14 and p=0.22, respectively) compared to the controls. We observed that the cognitive complaints of the patients had disappeared by the one-year follow-up.

CONCLUSION: In our patients with brain fog, most of whom had mild COVID-19, we observed that among all cognitive functions, memory domain was most affected compared to the controls. At the one-year follow-up, COVID-related brain fog had disappeared.

Keywords: Long COVID, brain fog, executive functions, memory, mental processing speed

INTRODUCTION

Cognitive complaints are an important cause for referral to neurology outpatient clinics in people recovering from coronavirus disease-2019 (COVID-19).[1,2] The expression "*brain fog*" is generally used to describe mental slowing, confusion, interruptions in thought and attention. This phenomenon is frequently reported by patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection after the acute period, and is called "*post-COVID brain fog*". Although the pathophysiology of brain fog is not clearly known, it has been claimed that neurogenic inflammation may play a role in its background.[3] In some recent publications, it has been shown that there was an increase in protein in the cerebrospinal fluid of those patients with post-COVID brain fog even after months, and some findings pointing to inflammation were observed.[4] Whether these findings are indicative of an overstimulated systemic immune reaction or a consequence of an intrathecal immune response has not been discerned to date.

In terms of clinical features; it has been observed that some patients experience mental slowdown, confusion, an inability to focus, an inability to find words, and short-term memory and planning problems after

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the COVID-19 infection has passed.[5,6] It is known that these cognitive complaints can persist even months after patients have recovered from their signs of infection, and they are then considered to be part of a prolonged (long) COVID or post-COVID syndrome.[7,8] It has been reported that cognitive impairment is more prominent in individuals with severe disease.[6,9] It is a matter of debate whether COVID-19 will cause cognitive sequelae in the long term. However, it has already been seen that patients lose functionality in their work, school and other daily life activities. For many patients, these cognitive problems are a source of additional anxiety. It is important in many ways to define the mental problems which patients experience, to determine their details, and especially to know their prognosis. If this phenomenon is better understood, first of all, appropriate management of patients can be provided and it will be possible to distinguish COVID-related cognitive problems from other diseases. On the other hand, those patients who need follow-up will be identified and unnecessary medical applications will be prevented for others.

Cognitive impairment associated with SARS-CoV-2 infection has been reported in many studies and reviews.[1,2,5-14] In some of these publications, an objective neuropsychological criterion revealing cognitive impairment was lacking, while in others, general cognitive screening tests such as the mini-mental test (MMSE) and the montreal cognitive assessment (MoCA) were used. Although there are a couple of large field studies pointing to cognitive dysfunction or memory issues after COVID-19, studies which report detailed neurocognitive testing and that also present objective data are relatively few.[14] Impairments in attention, executive functions, and short-term memory are evident in test-based examinations.[6,12,14] It is noteworthy that mental arithmetic, abstract thinking, language and visuospatial skills are less commonly evaluated. However, in our daily practice, it is observed that a substantial number of patients complain of not being able to calculate or of having difficulty in speaking. The combination of clinically heterogeneous, i.e. mild, severe and critical COVID-19 cases, in these study groups constitutes an important limitation in the literature to date.

In this study, we aimed to make a complete neurocognitive evaluation, instead of focusing on certain cognitive areas, in those patients who had COVID-19 which was not severe enough to require intensive care and who then applied to neurology due to cognitive complaints. For this purpose, we arranged one-to-one interviews with these patients and applied standard tests which have been frequently used and validated for our society. These test results are presented in comparison with age-matched healthy controls. After one year, all patients were interviewed on the phone, their complaints were re-examined and information about the further course of their brain fog was clarified.

MATERIALS AND METHODS

Subjects

All adult patients who applied with neurological complaints after COVID-19 were screened. The exclusion criteria were a diagnosis of dementia, malignancy, brain surgery, or other central nervous system diseases in the pre-pandemic period.

The diagnosis of COVID-19 in all patients was confirmed by polymerase chain reaction from nasopharyngeal swab samples. Among these patients, those who described brain fog were identified. A neurocognitive test battery was applied to those patients who agreed to a detailed examination. A control group of age-matched healthy individuals was used for comparison.

Informed consent was obtained from all participants. This study was carried out in accordance with the Declaration of Helsinki and under the approval of the TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (approval number: 118/102-28/4/21).

Data Collection

Age, sex, time of SARS-CoV-2 infection, disease severity, the need for hospitalization, comorbidities, and current neurological complaints were recorded for all patients.

Neurocognitive assessment consisted of the following tests: the mini-mental test (MMSE), the enhanced cued recall test (recall test), the verbal fluency, the categorical fluency, digit span, recalling the months backward, clock-drawing, arithmetic operations, a trail making test, copying cubes, intersecting pentagons, and proverb interpretation. This battery of tests was applied to the patients and their age-matched controls. We aimed to evaluate the general mental states of the participants' memory, language skills, attention, complex attention, visuospatial skills, arithmetic skills, executive functions and abstract thinking skills. The mini-mental test was scored over 30 points, the recall test out of 48 points, the fluency tests by the number of words that could be counted in one minute, the digit span by the number of digits which could be repeated without error, the months backward test by the countdown time of the months (in seconds), the clock drawing test over 4 points, the arithmetic operations over 2 points, the abstract thinking over 2 points, the copying cubes and intersecting pentagons as "*fail*" or "*pass*", and the trail making tests were scored by time (in seconds).

For cases of clinical necessity, brain magnetic resonance imaging (MRI) of the patients were requested.

At the end of one year, the patients who had undergone neurocognitive testing were contacted by phone and questioned as to whether their cognitive complaints had persisted. Those patients whose complaints continued were invited to the department and re-evaluated with the same cognitive tests.

Statistical Analysis

Student's t-test was used to compare normally distributed parameters and the Mann-Whitney U test was used for non-normally distributed parameters. The chi-squared test was used to compare ratios. Analyses were performed using the SPSS v20 program. Results with $p<0.05$ were considered to be significant.

Results

General Characteristics of the Study Group

Between April, 2020 and September, 2021, ninety-five COVID-19 patients who applied with neurological complaints were identified (n=95). Of these, 40% had cognitive impairments (n=38). Sixteen of these patients agreed to further examination and to having a neurocognitive test battery. The mean age of the test group (n=16) was 37.4±13.0 years [standard deviation (SD)]. Four of the patients were male and 12 were female. The median years of education of the patients was 15 years

[interquartile range (IQR)=2]. All but two were infected during the pre-vaccination period and were treated with favipravir. Disease severity was found to be mild in 15 patients and moderate in one patient. The patient who had moderate COVID-19 was hospitalized for 12 days and received nasal oxygen therapy during this period. There were no patients who needed intensive care.

The mean age of the control group (n=15) was 36.7±11 (SD), and their median years of education was 15 years (IQR=4). There was no statistically significant difference between these parameters (p>0.05).

Neurocognitive Assessment

The cognitive test results of the patients and controls are given in Table 1.

It was seen that post-COVID patients were no different from the controls in terms of their general cognitive performance. There was no difference between the patients and the controls in their enhanced cued recall test total scores. When spontaneous recall was evaluated separately, it was observed that the patients had statistically significantly lower scores (p=0.03). Attention and complex attention skills assessed by digit span tests, as well as verbal language skills were found to be similar in the two groups. Although executive functions and central processing speed (trail making A, B and recalling the months backward tests) were lower in the patient group, the differences were not statistically significant (p=0.07; p=0.14 and p=0.22, respectively). There was no difference between the patients and the controls in their abstract thinking or visuospatial skills.

When the patient results were assessed individually rather than as a group, it was seen that almost all the results were "*normal*" according to the normative thresholds, and only one patient could not complete the trail making B-test. In other words, despite subjective complaints, post-COVID patients had no supra-threshold impairment reflected in the detailed cognitive test results.

There were 5 patients who underwent brain MRI after cognitive evaluation. No imaging findings were found in three of these patients. Non-specific hyper-intensities in the frontoparietal subcortical white matter were reported in one. In one patient, hyper-intense lesions were detected in the right frontoparietal and left callososeptal interface (Figure 1).

Clinical Follow-up

Sixteen patients who underwent neurocognitive evaluation were contacted by phone at the end of the first year. They were asked if their cognitive complaints had persisted. Except for one patient, all of the group stated that their complaints had disappeared after a few months (median 120 days) and they had recovered to their former state. Only one patient stated that his complaints still continued. This patient was invited to the outpatient clinic and the tests were repeated. It was observed that both the first tests and the second evaluation made one year later were within normal limits and did not show any temporal changes. It was discovered that this patient was also diagnosed with anxiety disorder and treatment was started.

DISCUSSION

This study revealed the following findings which may correspond to the daily cognitive complaints of post-COVID patients: i) Patients had normal "*encoding*", but spontaneous recall was significantly low. ii) There were differences between the patient groups, although not statistically significant, indicating a decrease in executive functions and mental processing speed. iii) Almost all of the patients were within the "*normal*" range when standard tests with normative data were used. iv) By the end of one year, the symptoms of brain fog had disappeared.

Memory dysfunction is one of the most frequently reported cognitive symptoms in the COVID-19 literature.[6,10,12,14,15] In this study, the enhanced cued recall test was applied to assess memory. This test is a validated memory test used successfully in Turkish samples.[16,17] It offers the chance to observe the patient's spontaneous recall and their recall with a cue. In our patient group, there was no difference in the total scores (total items remembered before and after the cue) when compared to the healthy controls. However, spontaneous recall was found to be significantly lower. In other words, the *learning* process took place in the patients' brains, but there was difficulty in accessing that information. As the secondary causes which may explain this difficulty,

Table 1. Neurocognitive test results of the patient and control groups

	Patients	Controls	p
MMSE, median (IQR)	30 (2)	30 (1)	0.48
Recall, median (IQR)	48 (1.5)	48 (1)	0.62
Recall spontaneous, median (IQR)	36.5 (7.8)	43 (3)	**0.03**
Digit span forward, median (IQR)	5.5 (2)	5 (1.25)	0.37
Digit span backward, median (IQR)	4 (3.25)	4 (2)	0.71
Phonemic fluency, median (IQR)	17 (6)	18 (5)	0.46
Categorical fluency median (IQR)	24 (5.5)	25 (6)	0.9
Months backward, median (IQR)	13.5 (9.8)	11.5 (4.5)	0.22
Clock drawing, median (IQR)	4 (1)	4 (0)	0.15
Arithmetic, median (IQR)	2 (1)	2 (0)	0.13
Trail making A, seconds median (IQR)	32 (24)	22.5 (13.5)	0.07
Trail making B, seconds median (IQR)	87 (79.5)	41.5 (67.8)	0.14
Abstract thinking, median (IQR)	2 (0)	2 (0)	0.39
Copying cubes and intersecting pentagons	pass	pass	1

MMSE: Mini-mental state examination, recall test: Enhanced cued recall test, IQR: Interquartile range.

factors such as attention, concentration and motivation should be considered. However, there was no significant difference in attention and complex attention criteria in our patient group when compared to the healthy controls. This suggests that the impairment is primarily the effect of COVID-19 on memory itself.

It was observed that our patients had relatively low central processing speeds and executive functions, but the differences in these domains did not reach statistical significance. Impairments in executive functions and attention areas have been frequently reported in COVID-19-related brain fog, therefore our patients' results being similar to our controls' results can be explained by our relatively small sample size.[6,12,14,15]

In a recent systematic review, the neurocognitive status in mild, moderate, severe COVID-19 and mixed patient groups were examined separately.[15] It was seen that 13 out of the 19 studies included in the review used first-level tests such as MoCA and MMSE. In two of the six studies in which second-level tests, i.e. detailed cognitive tests, were conducted, face-to-face standard evaluation was not possible and remote evaluation methods were applied. It was also evident that the specific cognitive tests used in these studies varied considerably. There were different findings about the relationship between cognitive complaints and COVID-19 severity. There are some studies suggesting that cognitive impairment was more common in cases of severe disease; some saying that it was more common in mild-moderate cases; and others saying it was independent of disease severity.[7,10,15] We think that it is important to evaluate mild COVID cases separately from severe cases in order to exclude post-intensive care syndrome. It is known that primary and secondary cognitive symptoms can develop just due to hospitalization in intensive care units.[18] Studies which evaluate mild COVID cases separately and qualify to enter into reviews are very few in number.[19,20] In addition, it was seen that general cognitive screening scales were used in these studies and there was no detailed neurocognitive examination data. In the study of Alemanno et al.[20], there were nine mild cases of COVID and the evaluation was made as early as 5-20 days. As can be seen, the literature on COVID-19-related brain fog is weak and limited. In our cohort, 16 patients were examined with detailed and *domain-specific* tests which were second level. These are standard tests which have been validated in Turkish society.

Ferrucci et al.[21] examined hospitalized COVID-19 patients with neuropsychological tests five months after discharge and found a decrease in mental processing speed in 41% of the patients. It was stated that the PO_2/FiO_2 value in the acute period was correlated with cognitive impairment, and cognitive deficits persisted at one-year follow-up.[21] We also observed a slight decrease in the central processing speeds in our own patients, but this difference was not significant. The fact that most of our patients were outpatients with mild disease severity without hypoxia may explain this difference. On the other hand, a global frequency reduction in EEG background activity (advanced analysis) at 4-6 months post-infectious was demonstrated in a pediatric sample of mild-to-moderate COVID cases.[22] In the aforementioned study, the patients did not clinically have central nervous system involvement due to COVID-19.[22] We think that the slowdown in global mental processes revealed by neuropsychological tests may be related to electrophysiological COVID findings.[23]

Arithmetic problem solving includes many cognitive steps. The recall of mathematical rules, associative recall, attention, sequencing, working memory and decision making are the main ones.[24] Despite the problems in performing calculations during daily life, our patients performed normally in these tests. This could be associated with higher attention and motivation during the neurocognitive testing, which is different from their daily routine. This points to the importance of *attention and vigilance* in mental arithmetic skills. In our patient group, no difference was found in visuospatial skills, abstract thinking skills or language-fluency tests when compared to the controls.

Seventy five percent of our patients describing brain fog were women. This finding is consistent with the literature.[7] It is predicted that this neurobiological difference between the sexes will provide information in understanding the neurotropic properties of this virus. In addition, 87% of our patients presenting with brain fog came from the period before the vaccination program had started. After the initiation of the vaccination program, it was observed that the number of applications with cognitive complaints decreased significantly. This finding supports the observation that COVID vaccines reduce prolonged COVID syndrome.[25]

The underlying mechanism being unknown, our study revealed that

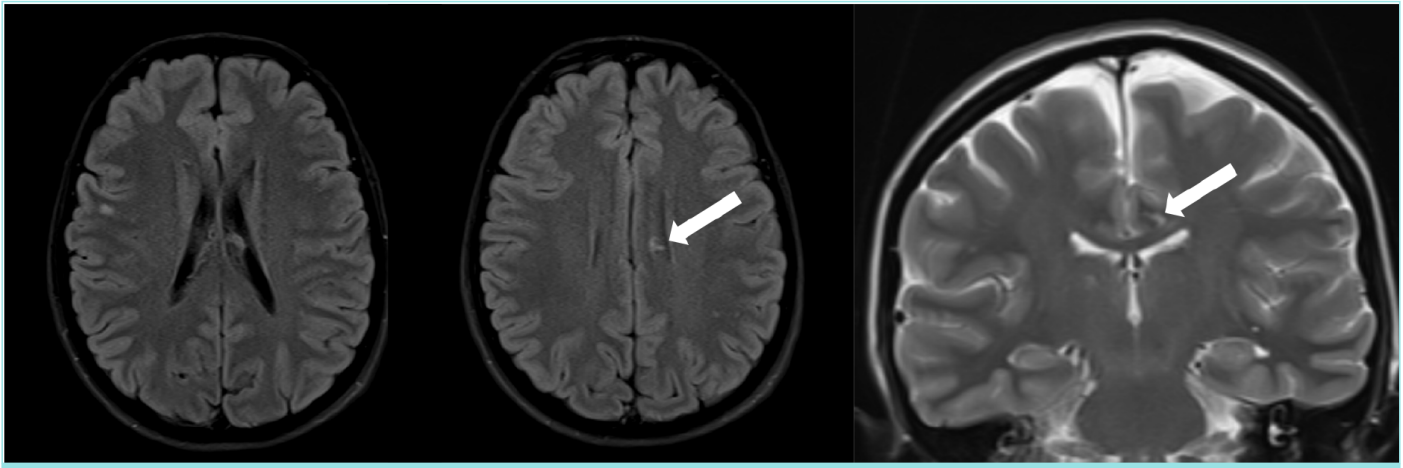

Figure 1. FLAIR images of a patient, right frontoparietal and left callososeptal (white arrows) hyper-intense lesions. The complaints of this 35-year-old patient were the inability to remember things to do, forgetting topics discussed at work in a short time, headaches and feelings of instability.

cognitive complaints disappeared in our patients and the patients had returned to their basal performances in daily life by the end of one year. We think that our data will provide an objective contribution to the COVID-associated brain fog literature for millions of people, especially those with mild cases.

Study Limitations

The neurocognitive test battery used in this study lasts approximately 45 minutes, but it may take longer depending on the patient's performance. This period resulted in a low number of patients who agreed to participate in these tests. Although there were 38 patients presenting with cognitive complaints, only 16 of them could be evaluated in detail. This relatively small sample size may have resulted in the statistical insignificance of the differences in the trail making test results.

Evaluating cognitive performance with normative references or controls may not be sufficient to detect actual changes in patients. This becomes more important in those patients with a high pre-morbid cognitive level. Ideally, patients should be assessed with their pre-COVID-19 and post-COVID-19 cognitive tests. Such a study design can only be achieved by using cognitive data obtained for other projects or large national databases.[19,26]

CONCLUSION

As of August, 2022, the SARS-CoV-2 pandemic had affected 590 million patients in the world and more than 16 million in our country (Türkiye). Residual respiratory diseases, severe or critically ill patients with many complications, will result in a serious disease burden in the chronic period of the pandemic. In addition, brain fog, which is a component of the long COVID-19 picture, appearing even after mild COVID-19, has taken its place as one of the important issues of the subacute and chronic processes. This study revealed the neurocognitive profiles of patients experiencing COVID-19-related brain fog in comparison to healthy controls. In our patient group, most of which consisted of mild COVID-19 cases, spontaneous recall was significantly lower, and there was a trend towards slowing in the central processing speeds and executive functions. By the one-year follow-up, COVID-associated brain fog had disappeared. It will be possible to elucidate all aspects of this clinical picture and to determine its relationship with neurodegenerative processes with larger-scale, longitudinal studies and pathological data.

MAIN POINTS

- Patients with post-COVID brain fog had normal *encoding*, but spontaneous recall was significantly low.
- There were decreases in executive functions and mental processing speeds in the patient group, although this was not statistically significant.
- Almost all of the patients were within the "*normal*" range when standard tests with normative data were used.
- By the end of one year, the symptoms of brain fog had disappeared.

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ETHICS

Ethics Committee Approval: This study was carried out in accordance with the Declaration of Helsinki and under the approval of the TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (approval number: 118/102-28/4/21).

Informed Consent: Informed consent was obtained from all participants.

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