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Investigation of cognitive decline in patients with COVID-19 syndrome within 12 weeks after infection

Hatice Seğmen, Keriman Oğuz

Department of Neurology, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences, İstanbul, Turkiye

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Corresponding Author: Hatice Seğmen, haticesegmen@hotmail.com

ABSTRACT

Aims: Recent findings suggest that COVID-19 may contribute to cognitive decline through neuroinflammatory and vascular mechanisms. To clarify the extent and underlying causes of these effects, we propose a study examining the cognitive outcomes of affected individuals. This study aims to investigate the effect of cognition in patients with COVID-19 within 12 weeks after infection.

Methods: A prospective study included 30 patients with COVID-19 within 12 weeks after COVID-19 and 30 healthy controls. The age, gender and educational status of the participants were recorded. These patients underwent montreal cognitive assessment (MoCA) test. Statistical comparisons were performed using Mann-Witney U test and Pearson Chi-square test.

Results: There was a statistically significant difference in age between the patients with COVID-19 and the control group (p=0.02). No statistically significant difference was found between the two groups in terms of gender (p=0.06). The total MoCA test score of the COVID-19 patient group was found to be statistically significantly lower than the control group (p=0.00). The education level of the patients with COVID-19 was found to be statistically significantly lower than the control group (p=0.05).

Conclusion: The results suggest that cognitive decline is a prolonged effect within 12 weeks after COVID-19. Emerging research suggests that COVID-19 may lead to cognitive impairments, including memory deficits and executive dysfunctions. Neuroinflammatory mechanisms and vascular complications are proposed as key contributors to these changes, highlighting the need for further investigation into the long-term neurological consequences of the infection.

Keywords: COVID-19 syndrome, cognitive decline, cognitive test, post-acute COVID syndrome

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus that causes a range of symptoms known as coronavirus disease (COVID-19).[1]

The cytokine storm in COVID-19 can cause a series of small punctate ischemias without causing significant neurological deficits. When these patients leave the hospital after an acute SARS-CoV-2 infection, it may present as memory impairment, loss of attention, or slowness of thinking. More than 80% of patients discharged from hospital after COVID-19 reported severe cognitive difficulties in their daily lives even 4 months later.[2] Therefore, if these patients still have cognitive problems, slowness of information processing, or attention deficit even months after hospital discharge, it would be beneficial to see a neurologist or undergo neurocognitive testing. Patients who score low on some cognitive tests may need to undergo brain rehabilitation to return to their baseline cognitive capacity levels. As a result, their risk of developing age-related cognitive decline in later life will be reduced.[3,4] MoCA is the most commonly used tool in the studies reported in reviews, so it may be a relevant screening tool for cognitive assessment after COVID-19. However, the recent development of other digital cognitive screening tools may provide other alternatives.[5]

Some patients develop symptoms such as fatigue, “brain fog,” or cognitive decline after the acute infection phase; this phase is often referred to as “long COVID”.[6]

The post-COVID-19 syndrome (PCS) is divided into two categories: (1) acute or persistent symptomatic acute post-COVID-19, which includes symptoms and abnormalities present 4–12 weeks after COVID-19; and (2) chronic PCS, which includes symptoms and abnormalities that persist or are present beyond 12 weeks from the onset of acute COVID-19.[7]

In this study, we planned to investigate cognitive test in patients with COVID-19 within 12 weeks after COVID-19 and healthy volunteers.

METHODS

Consent was obtained from these participants in accordance with the Helsinki Declaration. Permission to conduct the study was obtained from the Ministry of Health and the Ethics Committee of İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences (Date: 29.01.2021, Decision No: KAEK/2021.01.29).

For the study, 30 patients whit COVID-19 within 12 weeks after COVID-19 who applied to the Neurology outpatient clinic of İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences between February 2021 and September 2021 were randomly selected. These patients underwent montreal cognitive assessment (MoCA) test. As the control group, 30 randomly selected people, male and female, over the age of 18, who had never had covid, who applied to the outpatient clinic, were taken and the MoCA test was performed. The age, gender and educational status of the participants were recorded. Patients with other neurological and psychiatric diseases were excluded from the study. The case group and the control group were compared in terms of age, gender, educational status, MoCA test results.

Statistical Analysis

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 24 (İBM Corp., Armonk, NY). All data are presented as mean±standard deviation. Group differences in demographic data and neuropsychological variables were evaluated using the independent sample t-tests. The Mann-Whitney U test was used as a nonparametric equivalent of the Student's t-test for non-normaly distributed data. Catagorical variables were expressed as counts and percentages. The Wilcoxon rank-sum test and Maental-Haenszal X^2 test were used to compare of two groups. All results were quoted as 2-tailed P values, with statistical significance set at $p<0.05$.

RESULTS

The study included 30 patients with COVID-19 and 30 healthy controls. The mean age of the patients with COVID-19 was 43.3±12.9, and the mean age of the control group was 35.6±11.4 (Table 1). There was a statistically significant difference in age between the patients with covit-19 and the control group ($p<0.05$). The age of patients with COVID-19 was found to be statistically significantly higher than the control group (Table 2).

15 (50%) of the patients with COVID-19 were female and 15 (50%) were male. 22 (73.3%) of the subjects in the control group were female and 8 (26.7%) were male (Table 1). No statistically significant difference was found between the two groups in terms of gender ($p>0.05$) (Table 2).

The total MoCA test score average of the patients with COVID-19 was 43.3±12.9, and the total MoCA test score of the control group was 35.6±11.4 (Table 1). A statistically significant difference was found between the patients with COVID-19 and the control group in terms of the total MoCA test score ($p<0.05$). The total MoCA test score of the COVID-19 patient group was found to be statistically significantly lower than the control group (Table 2). In the MoCA test subcategories in the COVID-19 patient group, except for naming, the score of the COVID-19 group was found to be statistically significantly lower than the control group in all categories. No statistically significant difference was found between the two groups only in the naming category.

Of the patients with COVID-19, 1 (3.3%) was uneducated, 15 (50%) were primary school graduates, 11 (36.7%) were high school graduates, and 3 (10%) were university graduates. Of the subjects in the control group, 1 (3.3%) was uneducated, 2 (6.7%) were primary school graduates, 6 (20%) were high school graduates, and 21 (70%) were university graduates. The education level of the patients with COVID-19 was found to be statistically significantly lower than the control group ($p<0.05$) (Table 2).

DISCUSSION

Since the beginning of the coronavirus disease 2019 pandemic, many persistent neurological sequelae, including cognitive decline, have been recognized as part of the post-acute COVID syndrome. The reticular activating system (RAS) in the brainstem controls the sleep-wake cycle and executive attention.[8] The brainstem also houses the raphe nuclei and locus coeruleus, which are the primary source of serotoninergic and noradrenergic neurons in the brain, respectively.[9,10] The ventral tegmental area and substantia nigra are also located in the midbrain of the brainstem, which supply dopaminergic neurons to higher brain regions.[11,12] These neurotransmitters originating in the brainstem have been shown to be associated with a wide range of neurological disorders, including depression, anxiety, sleep and cognitive disorders, headache, fatigue, myalgia, and pain perception.[13,14] Therefore, invasion of SARS-CoV-2 into the brainstem may disrupt neurotransmitter systems in the brain, causing various neurological symptoms.

Long COVID has a wide range of manifestations, including cardiopulmonary complications, persistent fatigue, and neurocognitive dysfunction among various persistent syndromes.[15-21] Although there is no universally accepted definition, in December 2020, the United Kingdom (UK) National Institute for Health and Care Excellence guidelines defined long COVID as the persistence of symptoms for more than 4 weeks after SARS-CoV-2 infection.[22] This term consists of two phases: a ongoing symptomatic post-acute phase (4–12 weeks) that persists according to the duration of symptoms and a chronic phase PCS (>12 weeks). More recently, the World Health Organization has provided a case definition for post-COVID-19 status[23] which is used to refer to the persistence of symptoms for more than 3 months after SARS-CoV-2 infection, lasting at least 2 months, and not explained by another illness.[7]

Post-acute COVID-19 status is defined as persistent symptoms that persist for at least 8 weeks, usually occurring within 12 weeks from onset in individuals with confirmed or probable SARSCoV-2 infection in the past and that cannot be explained by an alternative diagnosis.[24] Fatigue and cognitive

Table 1. Demographic data and MoCA test results of the participants

	COVID (-) (n=30)		COVID (+) (n=30)		Total	
	n	%	n	%	n	%
Gender						
Female	22	73.3	15	50	37	61.7
Male	8	26.7	15	50	23	38.3
Education						
1 uneducated	1	3.3	1	3.3	2	3.3
2 elementary	2	6.7	15	50	17	28.3
3 high school	6	20	11	36.7	17	28.3
4 university	21	70	3	10	24	40
COVID						
1 COVID (-)	30	50	_	_	30	50
2 first month	_	_	9	30	9	15
3 second month	_	_	11	36.7	11	18.3
4 third month	_	_	10	33.3	10	16.7
Age	35.6±11.4 med:30.5 min:24 max:69		43.3±12.9 med:39 min:19 max:65		39.4±2.6 med:26 min:19 max:30	
MoCA	25.7±2.6 med:26 min:19 max:30		17.3±5.9 med:19.5 min:5 max:28		21.5±6.2 med:23 min:5 max:30	

Min: Minimum, Max: Maximum, SD: Standard deviation, Med: Median, Mean±standard deviation, MoCA: Montreal cognitive assessment test

Table 2. Comparison of demographic data and cognitive test score between groups

	Total	COVID (+)	COVID (-)	Test statistic	p*
	n=60	n=30	n=30		
Age	39.4±2.6	43.3±12.9	35.6±11.4	Z: -2.265	0.02[a]
MoCA	21.5±6.2	17.3±5.9	25.7±2.6	Z: -5.61	0.00[a]
Gender					
Male	23 (38.3)	15 (50)	8 (26.7)		
Female	37 (61.7)	15 (509	22 (73.3)	X^2: 3.45	0.06[b]
Education					
1 uneducated	2 (3.3)	1 (3.3)	1 (3.3)		
2 elementary	17 (28.3)	15 (50)	2 (6.7)		
3 high school	17 (28.3)	11 (36.7)	6 (20)		
4 university	24 (40)	3 (10)	21 (70)	X^2: 24.91	0.00[b]

Mean±standard deviation, MoCA: Montreal cognitive assessment test, a: Mann-Whitney U test, b: Pearson Chi-square test

impairment have been reported to be some of the most common complaints of PCS.[25]

In a systematic review and meta-analysis of 81 studies, it was found that approximately one-third of the individuals included experienced persistent fatigue 12 or more weeks after COVID-19 diagnosis and more than one-fifth of the individuals exhibited cognitive decline.[26] In our study, we evaluated cognitive functions in individuals who were within 12 weeks after COVID-19.

Most studies included in the current review used the MoCA instead of the MMSE as a general cognitive screening test.[27,28] These studies reported that the MoCA assessment was more sensitive than the MMSE in detecting cognitive deficits in patients who tended to perform worse on this task compared with uninfected controls. In our study, we used the MoCA test for cognitive function assessment.

Another study showed that cognitive decline (mainly attention and executive function impairments) was reported in 28–56% of patients with mild or asymptomatic COVID-19 and was associated with reduced cortical thickness in the right gyrus rectus and language-related areas.[29] Another published article showed that changes in working memory, set shifting, divided attention and processing speed were not associated with intubation length, psychiatric and clinical diagnosis in a cohort of 57 patients who recovered from moderate/severe COVID-19.[30] In our study, in the MoCA test subcategories in the COVID patient group, the COVID group had a statistically significantly lower score than the control group in all categories except naming. No statistically significant difference was found between the two groups only in the naming category.

Previous studies have reported that cognitive decline in post-acute COVID-19 syndrome may be associated with risk factors such as advanced age, low education level, pre-morbid delirium, male gender, and history of neuropsychiatric disease.[31,32] In our study, consistent with the literature, higher age and lower education level were found in patients with COVID-19 compared to the control group.

Studies have consistently identified attention, memory, and executive functions as the cognitive domains most affected by COVID-19 infection. Many studies have also reported neuroimaging, blood test deterioration, and neurophysiological abnormalities that could potentially reflect pathophysiological aspects of post-COVID cognitive impairment. Although patients with dementia are at high risk of COVID-19 infection, increasing evidence suggests that COVID-19 infection may increase the risk of Alzheimer's disease and that there is a bidirectional relationship between them. Post-COVID cognitive dysfunction is a common and multifaceted problem. Future explanations regarding long-term effects, mechanisms, and treatments will depend on the joint efforts of clinicians, researchers, and patients.

Limitations

There are some limitations to the study. In the study conducted on patients who applied to the outpatient clinic randomly, the difference in age and education level may be coincidental. There may be other factors such as low income level and depression that affect these results. Since there were no baseline cognitive data before the infection, we could not evaluate the cognitive change by comparing it with the previous status.

The effects of longer-term cognitive decline and their clinical significance remain unclear. For these reasons, it can be said that if there are people who complain that their cognitive decline has not returned to its previous level after having COVID, they should be examined in more detail and continued to be followed up clinically.

CONCLUSION

Our study examined cognitive decline in individuals who had contracted COVID-19 within the past 12 weeks, comparing them to a control group. Preliminary findings indicate a noticeable decline in cognitive functions among COVID-19 patients, aligning with previous research on this subject. However, given the multifactorial nature of cognitive impairment and its complex etiology, further studies with larger sample sizes and extended follow-up periods are necessary to confirm these observations and refine our understanding of post-viral cognitive outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

Permission to conduct the study was obtained from the Ministry of Health and the Ethics Committee of İstanbul Kanuni Sultan Süleyman Training and Research Hospital, University of Health Sciences (Date: 29.01.2021, Decision No: KAEK/2021.01.29).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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