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Olfactory Dysfunction and Cognitive Impairment After COVID-19

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Abstract

BACKGROUND/AIMS: The coronavirus disease-2019 (COVID-19) pandemic has brought to mind the long-known relationship between loss of smell, cognitive functions, and neurodegenerative processes and raised the question, "Can COVID-19 trigger or accelerate the development of neurodegenerative diseases?". This study aimed to investigate cognitive functions and their relationship with loss of smell, temporal changes in cognitive functions, and factors that may have an effect on this possible change in individuals with COVID-19.

MATERIALS AND METHODS: Individuals between the ages of 18-60, who had mild-moderate COVID-19 were included in the study within 3-6 months following the disease. COVID-19-related olfactory dysfunction and its duration were evaluated. Cognitive functions were assessed using the Addenbrooke's Cognitive Examination-Revised test battery and the Symbol Digit Modalities test. After six months, neuropsychological tests were repeated.

RESULTS: Ninety-seven patients who had COVID-19 (52 patients with COVID-19-related loss of smell and 45 patients without) were included in the study. Fifty patients were re-evaluated 6 months after their initial examination. Loss of smell was found to be continued for ≤3 months in 42 patients and >3 months in 10 patients. Neuropsychological test results showed that cognitive function was affected by loss of smell at the first examination. Additionally, the cognitive impact was more pronounced in the group with >3 months of smell loss than in the group with ≤3 months of smell loss. Six months later, test results were better than those at the first examination in both groups, regardless of loss of smell or not.

CONCLUSION: Our results indicate that cognitive function may be affected with or without loss of smell in patients with COVID-19, and that cognitive dysfunction and the duration of loss of smell may be related. It was found that cognitive functions were recovered substantially over time, and it was considered that COVID-19-related damage affecting cognitive functions was recoverable.

Keywords: Cognitive impairment, COVID-19, long-COVID, loss of smell, olfactory dysfunction

INTRODUCTION

Experiences during the coronavirus disease-2019 (COVID-19) pandemic revealed that neurological and neuropsychiatric symptoms related to the disease may develop over a wide spectrum and spread over time. A high frequency of cognitive complaints after COVID-19 was reported, and the effect of COVID-19 on cognitive function was almost invariably shown in many studies.[1-9] During the COVID-19 pandemic, olfactory dysfunction became a common symptom that was frequently observed and attracted attention.[10,11]

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Olfactory dysfunction may develop as a result of a wide range of factors and pathological events, ranging from viral infections including Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) to neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). Olfactory dysfunction is also a sensitive biomarker of neurodegenerative diseases.[12-17] It was suggested that a connection between SARS-CoV-2 infection and olfactory dysfunction may play a potential role in the development of neurodegenerative diseases or occurrence of predisposition to these diseases in individuals with COVID-19.[12]

Although it is not known whether SARS-CoV-2 is neurotropic and the extent of its damage to the central nervous system (CNS), several hypotheses have been suggested to clarify its entry into the CNS. First, SARS-CoV-2 probably proceeds via axonal/transsynaptic transport in olfactory neurons innervating the nasal epithelium and reaches the olfactory bulb, olfactory cortex, other structures in the temporal lobe, and possibly the brain stem.[18,19] The other hypotheses are that SARS-CoV-2 may spread to many parts of the brain by being transmitted into the cerebrospinal fluid surrounding the olfactory nerve bundles, enter the CNS hematogenously, and infect vascular endothelial cells, pericytes, and possibly neurons.[10,12,18,20,21]

It has been suggested that SARS-CoV-2, like other coronaviruses, may remain in certain neurons without causing acute toxicity, cause abnormal folding and aggregation of proteins, and lead to neurodegenerative processes that may arise in individuals who have COVID-19 within the subsequent years.[22-24] Coronaviruses affect endosomal cathepsins, cell surface transmembrane or serine proteases, and host proteases, such as furin and trypsin.[25,26] Most of these proteases have an important role in the degradation of altered neural proteins, such as alpha-synuclein, amyloid precursor protein, and huntingtin, and play a role in the pathogenesis of neurodegenerative diseases, such as PD and AD.[25,27] Another comment for clarifying the relation between COVID-19 and neurodegenerative diseases is that after entering the olfactory bulb, viral proteins are released by the replication of SARS-CoV-2, activating the release of proinflammatory cytokines; the resulting inflammatory environment also triggers oxidative stress mediators, leading to the loss of dopamine neurons or the aggregation of proteins, such as amyloid fibrils and α-synuclein responsible for the pathogenesis of PD and AD.[12,28-30]

The long-known relationship between loss of smell and cognitive function and neurodegenerative processes brings into mind the question of whether olfactory dysfunction in patients with COVID-19 can predict cognitive impairment. The answer to the question of whether COVID-19 will increase the risk of dementia in the future is not yet clear. In this study, we aimed to investigate the relationship between loss of smell and its duration and cognitive function in patients after COVID-19. The changes in cognitive function over time and the factors that may have affected this change were also investigated.

MATERIALS AND METHODS

Patients aged 18-60 years with COVID-19 and at least primary school graduates were included in the study within 3 to 6 months following the illness. The study participants were selected from relatives of patients who applied to the neurology outpatient clinic. The study was conducted prospectively. Patients were included in the study between August 2021 and October 2021.

Patients with a confirmed diagnosis of COVID-19 (positive SARS-CoV-2 polymerase chain reaction test result in nasopharyngeal swabs with viral symptoms), those with mild/moderate illness (with COVID-19 severity score between 1-4)[31] and those who did not require hospitalization at the intensive care unit were included in the study. Patients with a history of neurological disease, head trauma, systemic-induced cognitive impairment, psychiatric disease, and psychotropic drug use, diagnosed with depressive emotional disorder, a history of olfactory disorder symptoms that developed for any reason before COVID-19, a history of nasopharyngeal surgery, and in whom COVID-19-related encephalopathy developed were excluded from the study.

The participants were interviewed face-to-face, and the information forms developed for the study were completed. It was queried whether the patients had any complaints related to their sense of smell (anosmia, hyposmia, hyperosmia, parosmia, phantosmia or cacosmia) due to COVID-19, and if so, how long it continued/whether it still continues. The education level of the patients was categorized as primary school, high school, or university graduate, and their education periods were recorded. Whether the patient was currently smoking and their body mass index (BMI) were determined. BMI ≥30 kg/m^2 was considered obesity. History of hypertension, diabetes mellitus (DM), coronary artery disease, and chronic lung disease (chronic obstructive pulmonary disease, asthma) were recorded.

Cognitive functions were evaluated with Addenbrooke's Cognitive Examination-Revised (ACE-R) test battery, which evaluates orientation, attention, memory, verbal fluency, language, and visuospatial ability, and the Symbol Digit Modalities test (SDMT), which evaluates attention, concentration, and speed of information processing. In addition, the participants were evaluated using Beck's Depression Inventory, and patients with scores ≥17 (moderate and severe depressive mood disorder) were excluded from the study because there may have been confusion in determining cognitive dysfunctions. The tests were performed by a clinical psychologist that was blind to patient information.

Comparisons were made in terms of cognitive function between patients with and without olfactory dysfunction for ≤3 months and >3 months as well as between patients with and without COVID-19-related olfactory dysfunction. A part of the participants of the study were called for a check-up 6 months after the initial examination, their neuropsychological tests were repeated, and it was determined whether any changes in cognitive functions and smell-related complaints had occurred over time. Factors that may affect temporal changes in neuropsychological test results were examined.

The study was conducted in accordance with the Declaration of Helsinki and with the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval number: 116/16, date: 26.07.2021). Written informed consent was obtained from all patients who participated in the study.

Statistical Analysis

SPSS 23.0 software (Statistical Package for the Social Sciences, version 23.0 for Windows, SPSS Inc., Chicago, IL). Conformity of continuous variables to normal distribution was researched by Shapiro-Wilk test. Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for continuous variables and number (%) for categorical variables. Independent two-sample t-test was used if

continuous variables had normal distribution and Mann-Whitney U test was used if continuous variables did not have a normal distribution. In the comparison of two dependent groups, the paired two-sample t-test was applied for data with normal distribution, and the Wilcoxon test was applied for the data not having normal distribution. Pearson's chi-square test was used to assess categorical variables, and Fisher's exact test was used when chi-square test conditions were not met. A linear regression model was used to analyze the independent variables affecting the changes in ACE-R, SDMT, and ACE-R memory sub-scores. The statistical significance level was set as $p<0.05$ in the analyses.

RESULTS

Participants

Ninety-seven people (59 females, 38 males; mean age 40.2±10.8) who had COVID-19 were included in the study, and initial cognitive assessment was performed within 3-6 months following the illness (mean: 128.6±25.1 days). Fifty of the 97 patients were evaluated at the second examination 6 months later.

In 52 of the patients (53.6%), COVID-19-related loss of smell developed. Loss of smell continued for ≤3 months in 42 patients (80.8%) and >3 months in 10 patients (19.2%). In 2 of 10 patients, the duration of loss of smell was >12 months.

The demographic and clinical characteristics of the patients, ACE-R scores, ACE-R memory subscore, and SDMT scores at the first examination and during the checkup after 6 months are presented in Table 1.

Loss of Smell

No statistically significant difference was detected between patients with and without COVID-19-related loss of smell in terms of demographic characteristics, comorbid conditions, and diseases, ACE-R score, SDMT score, and ACE-R memory subscore in the first and second examinations (Table 2).

The patients in whom loss of smell continued for more than 3 months had lower ACE-R scores in the first examination and lower SDMT scores in their checkups after 6 months compared with the patients in whom loss of smell continued for 3 months or less ($p=0.018$ and $p=0.044$, respectively) (Table 3).

Olfactory dysfunction persisted 12 months after COVID-19 in 2 patients. In a 47-year-old female patient who was a high school graduate, the ACE-R and SDMT scores in the first examination were significantly lower than the group averages. The test scores of another 19-year-old female patient were lower but not as significant as those of the first patient. An increase was found in the test scores of both patients in the second examination after 6 months, but a significant decrease in the test scores of the first patient was observed.

Changes in Cognitive Function After COVID-19 within the 6-Month Period

Fifty of the 97 patients whose initial examinations were performed were re-evaluated after 6 months (29 patients with loss of smell, 21 patients without loss of smell).

ACE-R scores in the second examination were found to have a statistically significant increase compared with ACE-R scores in the first examination in all patients with COVID-19 and in the subgroups with and without olfactory dysfunction ($p<0.001$, $p<0.001$ and $p=0.001$, respectively). In the ACE-R scores at the second examination, a statistically significant increase was observed in the patients with loss of smell lasting for ≤3 months and for >3 months ($p<0.001$ and $p=0.017$, respectively) (Table 4).

An increase was found in ACE-R memory subscore in the second examination compared with the first examination in all patients with COVID-19 and in the subgroups with and without loss of smell ($p<0.001$, $p<0.001$ and $p<0.001$, respectively). It was observed that there was a statistically significant increase in ACE-R memory sub-scores in both patients with 3-month loss of smell lasting ≤3 months and patients with >3-month loss of smell lasting >3 months ($p<0.001$ and $p=0.016$, respectively).

Table 1. Demographic and clinical characteristics of patients with COVID-19

	Patients with COVID-19, (n=97)
Age (years)	40.24±10.80
Gender	
Female	59 (60.8)
Male	38 (39.2)
Years of education	11.89±4.30
Level of education	
Primary school	31 (32)
High school	27 (27.8)
University	39 (40.2)
COVID-19 severity score	
1	23 (23.7)
2	66 (68)
3	4 (4.1)
4	4 (4.1)
Smoking	28 (28.9)
Obesity (BMI >30 kg/m^2)	23 (23.7)
Hypertension	14 (14.4)
Diabetes mellitus	9 (9.3)
Coronary heart disease	2 (2.1)
Chronic lung disease	2 (2.1)
Loss of smell	52 (53.6)
Loss of smell ≤3 months	42 (43.3)
Loss of smell for 3-12 months	8 (8.2)
Loss of smell >12 months	2 (2.1)
Loss of taste	46 (47.4)
Forgetfulness	79 (81.4)
ACE-R score (initial)	79.81±10.86
ACE-R memory subscore (initial)	15.32±4.42
SDMT score (initial)	49.68±17.05
ACE-R score (6 months later)	82.92±11.41
ACE-R memory subscore (6 months later)	17.24±3.99
SDMT score (6 months later)	54.69±16.71

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. BMI: Body mass index, ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modalities test, COVID-19: Coronavirus disease-2019.

SDMT scores in the second examination were found to have a statistically significant increase as compared with SDMT scores in the first examination in all patients who had COVID-19 and in the subgroups with and without olfactory dysfunction ($p<0.001$, $p<0.001$ and $p=0.002$, respectively). In SDMT scores at the second examination, a statistically significant increase was observed in patients with loss of smell lasting for ≤3 months ($p<0.001$). In patients with olfactory dysfunction lasting for >3 months, the change in the control SDMT scores was not statistically significant compared with that at the first examination (Table 4).

Independent variables that may affect changes in ACE-R, SDMT, and ACE-R memory sub-scores over 6 months (duration of olfactory loss ≤3 months or >3 months, age, gender, level of education, obesity, hypertension and DM) were evaluated using linear regression models. Regression models for the ACE-R, SDMT, and ACE-R memory subscore were not significant ($p=0.346$, $p=0.242$ and $p=0.281$, respectively) (Table 5).

Table 2. Comparison of demographic and clinical characteristics between patients with and without loss of smell

	Patients with loss of smell, (n=52)	Patients without loss of smell, (n=45)	p
Age (year)	38.73±10.77	41.98±10.69	0.141[1]
Gender			
Female	36 (69.2)	23 (51.1)	0.106[2]
Male	16 (30.8)	22 (48.9)	
Years of education	11.98±4.23	11.78±4.42	0.825[3]
Level of education			
Primary school	17 (32.7)	14 (31.1)	0.974[5]
High school	14 (26.9)	13 (28.9)	
University	21 (40.4)	18 (40)	
Smoking	33 (63.5)	36 (80)	0.117[2]
Obesity (BMI >30 kg/m^2)	9 (17.3)	14 (31.1)	0.176[2]
Hypertension	5 (9.6)	9 (20)	0.161[4]
Diabetes mellitus	4 (7.7)	5 (11.1)	0.729[4]
Coronary heart disease	2 (3.8)	0 (0)	0.497[4]
Chronic lung disease	2 (3.8)	0 (0)	0.497[4]
COVID-19 severity score (1-4)	2±0.68	1.75±0.60	0.312[2]
Forgetfulness	37 (71.2)	27 (60)	0.346[2]
ACE-R score (initial)	79.04±10.75	80.71±11.04	0.454[3]
ACE-R memory subscore (initial)	14.62±3.93	16.13±4.85	0.158[3]
SDMT score (initial)	49.33±16.40	50.09±17.94	0.828[1]
ACE-R score (6 months later)	83.36±11.87	82.33±11.04	0.760[1]
ACE-R memory subscore (6 months later)	17.07±3.91	17.48±4.19	0.729[1]
SDMT score (6 months later)	57.89±16.26	50.43±16.72	0.123[1]

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. [1]Independent two sample t-test, [2]Yates Correction, [3]Mann-Whitney U test, [4]Fisher's exact test, [5]Pearson's chi-square test. BMI: Body mass index, ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

DISCUSSION

The effect of COVID-19 on cognitive function was almost invariably demonstrated in many studies.[1-9] However, it remains unclear how often it affects, how long the effect lasts, whether it is permanent, and whether olfactory disorders that develop during the disease are markers for cognitive impairment. The reasons such as the fact that cognitive evaluations were performed in the acute phase of the disease or in the following months, the characteristics of the patients included in the study population, the variability in disease severity between studies, and the evaluation of different cognitive domains may have led to contradictory results.

In this study, there was no difference in cognitive function between patients with and without COVID-19-related loss of smell. However, in the first examination of patients whose loss of smell persisted for more than 3 months, ACE-R scores were found to be lower, indicating widespread cognitive dysfunction, including orientation, attention,

Table 3. Comparison of demographic and clinical characteristics among patients with loss of smell for ≤3 months or >3 months

	Patients with loss of smell for ≤3 months, (n=42)	Patients with loss of smell for >3 months, (n=10)	p
Age (years)	38.52±10.28	39.60±13.20	0.745[1]
Gender			
Female	29 (69)	7 (70)	1.000[2]
Male	13 (31)	3 (30)	
Years of education	12.40±4.31	10.20±3.55	0.114[3]
Level of education			
Primary school	12 (34.3)	2 (20.0)	
High school	10 (28.6)	3 (30.0)	0.658[4]
University	13 (37.1)	5 (50.0)	
Smoking	26 (61.9)	7 (70.0)	0.729[2]
Obesity (BMI >30 kg/m^2)	8 (19)	1 (10)	0.670[2]
Hypertension	5 (11)	0 (0)	0.569[2]
Diabetes mellitus	4 (9.5)	0 (0)	0.576[2]
Coronary heart disease	1 (2.4)	1 (10)	0.351[2]
Chronic lung disease	2 (4.8)	0 (0)	0.649[2]
COVID-19 severity score (1-4)	1.97±0.64	2.1±0.87	0.792[4]
Forgetfulness	29 (69)	8 (80)	0.704[2]
ACE-R score (initial)	80.76±9.96	71.80±11.44	**0.018[3]**
ACE-R Memory subscore (initial)	15.07±4.03	12.70±2.87	0.080[3]
SDMT score (initial)	50.90±16.15	42.70±16.60	0.157[1]
ACE-R score (6 months later)	84.95±11.49	78.57±12.59	0.159[3]
ACE-R Memory subscore (6 months later)	17.76±3.92	15.00±3.27	0.106[1]
SDMT score (6 months later)	61.43±14.95	47.29±16.43	**0.044[1]**

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. [1]Independent two sample t-test, [2]Fisher's exact test, [3]Mann-Whitney U test, [4]Pearson chi-square test; ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

Table 4. ACE-R and SDMT scores over a 6-month period and their relationship with loss of smell

	ACE-R score (initial)	ACE-R score (6 months later)	p	SDMT score (initial)	SDMT score (6 months later)	p
Patients with COVID-19	79.81±10.86	82.92±11.41	**<0.001***	49.68±17.05	54.69±16.71	**<0.001****
Patients without loss of smell	80.71±11.04	82.33±11.04	**0.001***	50.09±17.94	50.43±16.72	**0.002***
Patients with loss of smell	79.04±10.75	83.36±11.87	**<0.001***	49.33±16.40	57.89±16.26	**<0.001***
Patients with loss of smell ≤3 months	80.76±9.96	84.95±11.49	**<0.001***	50.90±16.15	61.43±14.95	**<0.001****
Patients with >3 months of loss of smell	71.80±11.44	78.57±12.59	**0.017***	42.70±16.60	47.29±16.43	0.688**

Data are presented as mean ± standard deviation. *Wilcoxon test, **Paired two sample t-test. Twenty-nine of the patients with loss of smell and 21 of the patients without loss of smell, 22 of the patients with olfactory dysfunction for ≤3 months and 7 of the patients with olfactory dysfunction for >3 months were evaluated 6 months after their initial examination. ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

Table 5. Linear regression models for the ACE-R and SDMT scores

Linear regression model of independent variables that may affect changes in ACE-R scores

	β_0 (95% CI)	β_1	t	p	r_1	r_2	VIF
Constant	2,380 (1.14-3,621)		4,048	0.001			
Patients with >3 months of loss of smell (no reference)	-0.371 (-0.97-0.228)	-0.272	-1,307	0.209	-0.196	-0.302	1,155
Age	-0.062 (-0.688-0.565)	-0.051	-0.208	0.837	-0.104	-0.050	1,597
Gender (no reference)	0.036 (-0.667-0.739)	0.027	0.108	0.915	-0.036	0.026	1,725
Education (reference: university)							
Primary school	0.514 (-0.215-1,242)	0.376	1,488	0.155	0.009	0.339	1,710
High school	0.461 (-0.236-1,158)	0.362	1,395	0.181	0.134	0.320	1,799
Obesity	-0.795 (-1,705-0.115)	-0.517	-1,843	0.083	-0.405	-0.408	2,106
Hypertension	0.380 (-1,017-1,778)	0.201	0.574	0.573	-0.056	0.138	3,262
Diabetes mellitus	-0.530 (-2,472-1,412)	-0.233	-0.576	0.572	-0.245	-0.138	4,385

F=1,219, p=0.346, R^2=36.5%, corrected R^2=6.6%, β_0: Unstandardized beta coefficient, β_1: Standardized beta coefficient, r_1: Zero order correlation, r_2: Partial correlation. As the ACE-R changes did not have a normal distribution, Ln conversion was applied.

Linear regression model of independent variables that may affect changes in SDMT scores

	β_0 (95% CI)	β_1	t	p	r_1	r_2	VIF
Constant	**1,619 (0.547-2,692)**		**3,218**	**0.006**			
Patients with loss of smell >3 months (no reference)	-0.467 (-1,093-0.159)	-0.382	-1,589	0.133	-0.423	-0.380	1,550
Age	-0.457 (-0.993-0.08)	-0.431	-1,813	0.090	-0.322	-0.424	1,518
Gender (no Reference)	0.082 (-0.61-0.774)	0.067	0.252	0.804	-0.102	0.065	1,892
Education status (reference: university)							
Primary school	0.152 (-0.544-0.848)	0.124	0.466	0.648	0.016	0.119	1,911
High school	0.182 (-0.502-0.866)	0.162	0.567	0.579	-0.043	0.145	2,192
Obesity	0.501 (-0.255-1,256)	0.384	1,413	0.178	0.159	0.343	1,983
Hypertension	0.808 (-0.413-2,029)	0.504	1,411	0.179	0.116	0.342	3,435
Diabetes mellitus	-1,320 (-2,978-0.339)	-0.688	-1,696	0.111	-0.050	-0.401	4,428

F=1,487, p=0.242, R^2=44.2%, corrected R^2=14.5%, β_0: Unstandardized beta coefficient, β_1: Standardized beta coefficient, r_1: Zero-order correlation, r_2: Partial correlation. Because the SDMT changes did not have a normal distribution, Ln conversion was applied. ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, CI: Confidence interval.

memory, verbal fluency, language, and visuospatial ability. Patients with persistent loss of smell for more than 3 months had lower SDMT scores on the second examination after 6 months. These findings indicated that the duration or persistence of loss of smell may be related to cognitive function rather than whether or not loss of smell development in patients with COVID-19. Our results can be interpreted as loss of smell may last longer in patients whose cognitive functions are affected in the early post-COVID-19 period; especially attention and concentration disorders and regression in the speed of information processing in patients whose loss of smell continues longer may develop within the further period. Patients in whom olfactory dysfunction continued for longer than 6 months after COVID-19 reported headache, mental clouding, or both more frequently. This finding was interpreted as cognitive impairment, and headache may be related to more severe olfactory loss.[32] Patients complaining of both dysgeusia and hyposmia during acute illness showed a lower improvement in memory tests than those without.[33] On the other hand, it has been suggested that advanced age and mild subtle cognitive deficits may be factors related to long-term olfactory dysfunction after COVID-19.[34]

In our study, an increase that reflects the recovery of cognitive function was found in the ACE-R and SDMT scores repeated after 6 months in the group of patients who had COVID-19, whether or not accompanied by loss of smell. This result was also considered to indicate the effect of COVID-19 on cognitive function. The recovery of cognitive function based on the checkup examination in both groups with and without loss of smell indicated that loss of smell may not be a factor directly related to the development of cognitive dysfunction. However, it was found that there was no significant recovery after 6 months in cognitive domains including attention, concentration, and speed of information-processing in the group with loss of smell lasting more than 3 months as compared with the group with loss of smell lasting less than 3 months; it was considered that the duration of loss of smell may be an effective factor for the recovery of cognitive functions after 6 months. From another perspective, our results indicated that cognitive function may have been affected in patients with COVID-19, but this effect may be recoverable, especially in patients with short-term loss of smell. Factors such as repair or compensation mechanisms are likely to be intact in patients with COVID-19, or that genetic or other predisposing factors do not exist in these patients, as in the other neurodegenerative diseases, may clarify the fact that the course of the damage leading to COVID-19-related cognitive dysfunction was not progressive and could be recovered.

The results of studies investigating the relationship between COVID-19 and cognitive dysfunction vary. Although no difference was found in terms of cognitive test results 4 months after SARS-CoV-2 infection in patients with mild-moderate COVID-19 in one study,[35] impairment in at least one cognitive domain was reported after 3 months in 78% of the patients in another study.[36] In a systematic review and meta-analysis, cognitive impairment developed in approximately 1/5 of the patients within 12 weeks or longer following COVID-19.[9] In another systematic review, cognitive deficit was found at a rate of 25%.[5] In studies on COVID-19-related cognitive affection, findings reflecting dysfunction of various cognitive domains, especially processing speed, executive functioning, memory, and attention disorders, were found.[3-5,33,37-40] The results of studies on the course of COVID-19-related cognitive dysfunctions over time also include differences.[5] It was reported that cognitive functions improved over time in certain studies.[33,40] Ongoing, prolonged, or permanent cognitive deficits were also identified.[1,33,41,42]

In our study, although olfactory dysfunction continued for longer than 3 months, it was observed that it recovered in most patients, and olfactory dysfunction persisted 12 months after COVID-19 in only 2 patients. In a 47-year-old female patient, the ACE-R and SDMT scores at the initial examination were significantly lower. The test scores of the second patient, a 19-year-old female, were lower but not as significant as those of the first patient. An increase in the test scores was found in both patients in the second examination after 6 months, but the significant decrease in the test scores of the first patient continued. Different brain areas associated with cognitive functions overlap with the olfactory pathways. The multiregional involvement of olfactory stimuli, including the orbitofrontal cortex, amygdala, and hippocampus, explains the relationship between odor perception and memory formation.[43-45] Various processes such as inflammation, alterations in neurogenesis of peripheral and central structures of the olfactory system, and functional changes in brain structures may explain the link between loss of smell and cognitive impairment, especially in patients with COVID-19-related prolonged olfactory disturbances.[46,47] Poor recovery of cognitive function may also be a sign of more severe derangement in cognitive circuits.

Greater severity of acute illness, duration of symptoms, advanced age, female sex, and preexisting comorbidities are frequently identified risk factors for cognitive affection.[5,9,38,42] In our study, it was determined that any of the factors, including age, gender, educational status, obesity, hypertension, and DM, were not effective on the temporal change in cognitive test results, and the improvement in cognitive functions developed independently of these factors. It was considered that mechanisms related to COVID-19 may play a role in the recovery of cognitive function, as well as in the affectation of cognitive function.

As the clinical severity of COVID-19 worsens, the impact on cognitive function may become more pronounced, with hypoxic brain damage coming into play. Therefore, patients with milder COVID-19 were included in the study to more accurately evaluate the direct effect of COVID-19 on cognition. Patients older than 60 years were not included in our study, considering the possibility of subclinical or mild cognitive impairments and the fact that cognitive impairments can be triggered more easily for various reasons in these patients.

Study Limitations

The evaluation of olfactory dysfunction based on self-reported assessment of the sense of smell, not clinical or electrophysiological tests, was a study limitation. However, this evaluation also made it possible to determine the loss of smell that is directly related to COVID-19. It is possible to detect pre-existing disorders that patients are unaware of using scent tests.

CONCLUSION

Our results indicate that patients with COVID-19 may possibly experience temporary and greatly improved cognitive impairment independent of olfactory dysfunction. Although loss of smell was not found to be associated with cognitive function, the relationship between prolonged and persistent olfactory dysfunction and cognitive impairment is remarkable.

MAIN POINTS

- COVID-19 may affect cognitive functions.
- Cognitive impairment caused by COVID-19 is mostly reversible.
- Olfactory dysfunction is a common symptom in the COVID-19 pandemic.
- Cognitive impairment after COVID-19 may occur with or without olfactory dysfunction.
- The duration of olfactory dysfunction is associated with cognitive impairment.

ETHICS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and with the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval number: 116/16, date: 26.07.2021).

Informed Consent: Written informed consent was obtained from all patients who participated in the study.

Authorship Contributions

Surgical and Medical Practices: C.D., F.A.E., A.C.Ü., Concept: C.D., F.A.E., B.G., A.C.Ü., H.G., Design: C.D., B.G., H.G., Data Collection and/or Processing: C.D., F.A.E., A.C.Ü., Analysis and/or Interpretation: C.D., B.G., H.G., Literature Search: C.D., A.C.Ü., H.G., Writing: C.D., B.G., H.G.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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