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ORIGINAL PAPER

Long-lasting cognitive effects of COVID-19: is there a role of BDNF?

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Abstract
Coronavirus disease 2019 (COVID-19) affects numerous systems of the body during the illness, and there have been long-lasting effects. BDNF plays an important role in synaptic plasticity and synaptic communication. According to the inclusion and exclusion criteria, 54 patients who had COVID-19 infection participated in this study. Thirty-six age-, sex-, body mass index (BMI)-, education level- and smoking status-matched healthy controls were included in the present study. All participants were individually administered the Stroop test and Visual Aural Digit Span Test Form B (VADS-B). Serum BDNF levels were measured by ELISA. Stroop test word reading spontaneous correction number and reading time, word color saying wrong number, spontaneous correction number and reading time, box color speaking spontaneous correction number and reading time, Stroop interference and speed factor duration were significantly higher in the COVID-19 group than in the control group. All scores of the VADS-B test were found to be significantly lower in the COVID-19 group. The mean serum BDNF levels were found to be 10.9 ± 6.9 ng/ml in the COVID-19 group and 12.8 ± 6.4 ng/ml in the healthy control group. Two-way ANOVA showed that the serum mean BDNF level was significantly lower in the COVID-19 group than in the control group. Gender had a significant effect on BDNF levels ($F = 12.21$; $p = 0.008$). The present study is the first to demonstrate the association between the role of serum BDNF and cognitive decline in patients with COVID-19 infection. Additionally, there is a significant role of male gender in terms of lower BDNF level and cognitive decline.

Keywords BDNF · Cognitive · COVID-19 · Impairment

Introduction

Severe acute respiratory syndrome (SARS-CoV-2) first appeared in Wuhan, China, in December 2019 and has been defined as coronavirus disease 2019 (COVID-19). COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. COVID-19 affects numerous systems of the body during the course of the illness, and there have been long-lasting effects of the disease after recovery. It has been well established that cognitive deficits can be seen during the illness, and moreover, cognitive problems have also been reported to be seen after recovery [2].

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The most common neurological symptoms in COVID-19 are headache, dizziness, anosmia, fatigue, myalgia, anorexia and ageusia. Severe neurological manifestations include confusion, seizures, cerebrovascular diseases, meningoencephalitis, acute necrotizing encephalopathy, posterior hemorrhagic encephalopathy syndrome, myopathy, radiculopathy, cerebellar ataxia, myoclonus and Guillain–Barre syndrome [3, 4]. The most common psychiatric symptoms of COVID-19 are as follows: depression, anxiety, sleep disorders, chronic fatigue syndrome and posttraumatic stress disorder symptoms [5]. Additionally, cognitive symptoms have recently been addressed [6].

SARS COV-2 binds to the ACE-2 receptor and enters epithelial cells in the lung. The S protein is cleaved by proteases such as TMPRSS2, cathepsin G, trypsin or disintegrin, and metalloprotease 17 (ADAM17) to facilitate viral entry. As a result, ACE-2 receptors are blocked. When ACE-2 activity is lost, the levels of angiotensin 1–7 and angiotensin 1–9 decrease. Based on these decreases, MAS/G protein-dependent receptors cannot be activated, vasodilation cannot occur, and cell protective mechanisms cannot be activated.

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All these mechanisms result in vasoconstriction, fibrosis, proliferation and atherogenesis, which are significantly associated with thrombophilia, microthrombosis, alveolar epithelial damage and respiratory failure [7].

BDNF is a protein member of the neurotrophin family, which includes neurotrophin 3 and neurotrophin 4. BDNF plays an important role in synaptic plasticity and synaptic communication [8]. The neurotrophic functions of BDNF are associated with memory, learning, sleep, appetite and neuronal survival. It is also well established that BDNF plays a critical role in hippocampal long-term potentiation (LTP), which is a long-term result of synaptic activity [9]. BDNF participates in many neurophysiological processes [10]. Angiotensin 1–7, which is produced by ACE-2, increases BDNF levels through the MAS receptor/PI3K/Akt/BDNF pathway. Given the decrease in the activity of ACE-2 receptors in the brain in COVID-19 patients, the level of BDNF may decrease, which causes neurodegeneration [11].

In the present study, we aimed to investigate whether there might be an association between cognitive impairment, which has been observed after mild COVID-19 infection, and serum BDNF levels.

Methods

Participants

The present study was conducted at Tekirdağ Namık Kemal University Hospital, Department of Psychiatry, between July 1, 2021, and January 1, 2022. The inclusion criteria were as follows: (1) a positive COVID-19 PCR test during the disease period and two negative tests postdisease, (2) having had mild disease according to the WHO's COVID-19 disease severity classification, (3) being between the ages of 18 and 50, (4) having a minimum education of 12 years, (5) having a BMI ≥ 18 and < 30 and (6) volunteering to participate in the study. The exclusion criteria included: (1) having a score above 7 on the Hamilton Depression Scale (HAM-D), (2) having a score of 6 or above on the Hamilton Anxiety Rating Scale (HAM-A), (3) having a psychiatric illness or a previous psychiatric illness and treatment, (4) having an alcohol or substance use disorder or a history of alcohol or substance use, (5) having current neurological disease or a history of neurological disease, (6) being treated with antidepressant, antipsychotic, mood stabilizer, antiepileptic, benzodiazepine and other drugs that may affect neurocognitive test evaluation, (7) presence of a known chronic inflammatory disease, cancer or autoimmune disease, (8) having acute or chronic infectious disease, (9) having a history of head trauma, (10) having a disease that increases intracranial pressure, (11) having a physical disease that affects the main organs of the body or that prevented neurocognitive testing, (12) presence of a defect in visual function that could not be corrected with lenses, (13) diagnosis of color blindness, (14) presence of a known allergy. According to the inclusion and exclusion criteria, 54 patients who had COVID-19 infection participated in the study. Thirty-six age-, sex-, BMI-, education level- and smoking status-matched healthy controls were included in the study. The inclusion criteria for healthy controls were as follows: (1) having no history of COVID-19 infection, (2) being between the ages of 18–50, (4) having a minimum education of 12 years, (5) having a BMI ≥ 18 and < 30 and (6) volunteering to participate in the study. The exclusion criteria for healthy controls were the same as those for the COVID-19 group. All participants were vaccinated with the BNT162b2 mRNA COVID-19 vaccine.

Assessment tools

Sociodemographical Form

This form was designed based on the literature. The form consisting of a total of 19 questions prepared in order to collect demographic information about the participants in the COVID-19 and healthy control groups and was completed by the researcher for all participants.

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HDRS) was established in 1960. It uses the 5-level rating method of 0 to 4 points. The total score is 0–78, and the depression level can be divided as follows: < 8 means no depression, 8–17 means possible depression, 18–24 means mild to moderate depression and > 24 means severe depression [12].

Hamilton Anxiety Rating Scale

The HAMA-14 is one of the most commonly used clinician-rated measurements of anxiety in studies of depression. The HAMA-14 is rated from 0 to 4 with general guidelines provided for distinguishing stagewise anxiety severity. It is a reliable and valid measure of the severity of anxiety in depressed patients and has become the standard in this field. A score higher than 7 indicates the presence of anxiety symptoms [13].

Neuropsychological tests

All participants in our study were individually administered the Stroop test and Visual Aural Digit Span Test Form B (VADS-B) by a supervised test practitioner to evaluate cognitive function.

Stroop test

The Stroop test was first developed by Stroop in 1935 as a neuropsychological test that measures focused attention, selective attention, response inhibition, resistance to interference and information processing speed in order to assess frontal lobe functions [14]. The reliability and validity study of the Turkish version of the Stroop test was performed by Karakaş et al. in 1999 [15]. The Stroop test consists of 5 cards, which are used as follows: In the 1st part, the subjects are asked to read the names of colors printed in black ink on the 1st card; in the 2nd part, they are asked to read the names of colors printed in colors different from the cards themselves as presented on the 2nd card; in the 3rd part, they are asked to say which color the colored circles are as presented on the 3rd card; in the 4th part, they are asked to say some neutral words printed in different colors; and finally, in the 5th part, they are asked to name the colors of the mismatching words printed in colors different from themselves. In each part, the total time for a subject to read words or say the colors, the number of correct answers, the number of errors and the number of spontaneous corrections are calculated. The Stroop interference score is calculated as the difference of 3 points, which is obtained by subtracting the duration of the 3rd part from that of the 5th part. The reading time of the 1st card with the color names printed in black, that is, the duration of the first part, shows the basic level of reading speed and is calculated as the speed factor [14].

Visual Aural Digit Span Test Form B (VADS-B)

The Visual Aural Digit Span Test Form B (VADS-B) is a neuropsychological test developed by Karakaş et al. based on the Visual Aural Digit Span test developed by Koppitz for use in children in 1977 to measure the attention and short-term memory function of the hippocampus and prefrontal cortex regions of the brain. One of the validity and reliability studies of the VADS-B was conducted by Karakaş et al. in 1995 [16]. The VADS-B is a test in which visual and aural stimuli are given and responses are received both orally and in writing. The VADS-B consists of consecutive number sequences, with the shortest sequence consisting of 2 numbers and the longest sequence consisting of 9 numbers. When the number sequences are repeated incorrectly, the subject is given a second try. This test consists of four subtests: aural oral (AO), visual oral (VO), aural written (AW) and visual written (VW). The VADS-B has a total of 11 points. Four of these scores consist of the basic scores obtained from each subtest, namely, AO, VO, AW and VW, and 6 of them are related to the combined scores of the aural input score (AO + AW), visual input score (VO + VW), oral expression score (AO + VO), written expression score (AW + VW), intrasensory integration score (AO + VW) and intersensory integration score (VO + AW).

Table 1 Comparisons of basic characteristics of groups

		Control group ($n = 36$)			Case group ($n = 54$)			p
		Mean. ± sd/n-%		Median	Mean. ± sd/n-%		Median	
Age		28.5 ± 5.4		28.0	29.9 ± 6.9		29.0	0.400[a]
Gender	Female	22	61.1%		31	57.4%		0.726[b]
	Male	14	38.9%		23	42.6%		
Weight		67.0 ± 13.2		62.5	69.6 ± 14.0		69.0	0.426[a]
Length		170.8 ± 7.5		170.0	169.8 ± 8.9		167.5	0.386[a]
BMI		22.8 ± 3.0		22.2	24.0 ± 3.4		23.9	0.115[a]
Marital status								
Married		9	25.0%		16	29.6%		0.631[b]
Single		27	75.0%		37	68.5%		
Divorced		0	0.0%		1	1.9%		
smoking status		7	19.4%		11	20.4%		0.914[b]
History of alcohol use		0	0.0%		0	0.0%		1.000[b]
History of Substance Use		0	0.0%		0	0.0%		1.000[b]
Psychiatric Illness		0	0.0%		0	0.0%		1.000[b]
Use of Psychiatric Drug		0	0.0%		0	0.0%		1.000[b]
History of Psychiatric Illness		0	0.0%		0	0.0%		1.000[b]
Hamilton Anxiety Rating Scale		0.28 ± 0.81		0.00	0.31 ± 1.02		0.00	0.849[b]
Hamilton Depression Rating Scale		0.06 ± 0.33		0.00	0.15 ± 0.76		0.00	0.791[b]

[a]Mann–Whitney U test

[b]Chi-square test or Fisher's exact test

Table 2 Clinical data of COVID-19

		n	% (%)
Number of COVID-19 infections	I	53	98.1
	II	1	1.9
Time passed after COVID-19	1–3 months	7	13.0
	3–6 months	6	11.1
	6 months-1 year	35	64.8
	More than a year	6	11.1
Symptoms of COVID-19 (During Infection)	Muscle pain	27	50.0
	Weakness	22	40.7
	Throat Ache	16	29.6
	Cough	15	27.8
	Headache	14	25.9
	Fever	13	24.1
	Loss of taste and smell	12	22.2
	Diarrhea	3	5.6
History of COVID-19 treatment	Favipiravir	43	79.6
	Enoxaparin Sodium	24	44.4
	Hydroxychloroquine	5	9.3
	Acetylsalicylic acid	2	3.7
	None	8	14.8

The total score is calculated as follows: AO + VO + AW + VW. A maximum of 9 points can be obtained for each subtest, a maximum of 18 points for each combined test and a maximum of 36 points in total [14].

Serum BDNF measurement

Peripheral blood samples (5–8 ml) were collected in a red-capped gel tube between 08:00 and 10:00 in the morning after 8 h of fasting. All peripheral blood samples were centrifuged at 1000 rpm for 15 min to obtain serum, and the obtained serum samples were stored in a deep freezer (− 80 °C). Serum BDNF levels were measured by ELISA. A commercial ELISA kit (Catalog No: E1302Hu) from Bioassay Technology Laboratory (Shanghai Korain Biotech Co., Ltd. Shanghai, China) was used for this measurement. The mass was measured using the sandwich ELISA principle.

Statistical analysis

Power analysis was used to determine the sufficiency of the sample size for the study. For the comparison of patient and control groups, the Mann−Whitney *U* test was performed for two independent samples. Additionally, the normal distribution assumptions were checked by using the Shapiro−Wilks normality test. In correlation analysis, Spearman's coefficient of correlation was used for non-normally distributed data or ranked data. Otherwise, Pearson's coefficient of correlation can be used for normally distributed data. Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Two-way ANOVA was used to compare serum BDNF levels between groups. Specifically, sex and group were selected as fixed factors, and the serum BDNF value was selected as the dependent variable. A post hoc Tukey test was used for comparisons.

Power analysis

To calculate the power of the study, the Mann−Whitney *U* test results were used. The effect size was derived by G*Power statistical software. The sample size of 72 achieved 91.6% power to detect an effect size of 0.83 using a Mann−Whitney *U* test with a significance level (alpha) of 0.05. A sample size of 90 was considered, and the power was approximately 96% at the alpha level.

Results

Sociodemographical and clinical care

There was no significant difference between the two groups in terms of sociodemographic characteristics and HAM-D and HAM-A scores. The data are shown in Table 1.

The COVID-19 clinical characteristics are presented in Table 2. The duration of recovery was found to be as follows: 35 (64.8%) patients had COVID-19 6–12 months before participating in the study (Table 2).

Table 3 Comparisons of data of Stroop and VADS-B tests

	Control group ($n=36$)		Case group ($n=54$)		p
	Mean ± sd	Median	Mean. ± sd	Median	
Stroop					
Word Reading					
Number of correct word	48.0 ± 0.0	48.0	48.0 ± 0.1	48.0	0.414
Number of wrong word	0.00 ± 0.00	0.00	0.02 ± 0.14	0.00	0.414
Spontaneous correction	0.00 ± 0.00	0.00	0.13 ± 0.39	0.00	**0.040**
Reading time	16.3 ± 2.7	15.7	19.1 ± 3.7	18.3	**< 0.001**
Saying The Word's Color					
Number of correct word	48.0 ± 0.2	48.0	47.5 ± 1.1	48.0	0.06
Number of wrong word	0.03 ± 0.17	0.00	0.46 ± 1.13	0.00	**0.023**
Spontaneous correction	0.33 ± 0.68	0.00	0.78 ± 0.92	1.00	**0.009**
Saying time	28.5 ± 5.0	28.5	36.2 ± 10.8	33.0	**< 0.001**
Saying The Box's Color					
Number of correct word	24.0 ± 0.0	24.0	23.9 ± 0.4	24.0	0.246
Number of wrong word	0.0 ± 0.0	0.0	0.1 ± 0.4	0.0	0.246
Spontaneous correction	0.0 ± 0.0	0.0	0.2 ± 0.4	0.0	**0.010**
Saying time	10.2 ± 1.3	10.0	12.1 ± 2.2	11.7	**< 0.001**
Interference	8.0 ± 3.8	8.3	11.7 ± 6.3	9.7	**0.010**
The speed factor	7.9 ± 1.2	7.7	9.3 ± 1.5	9.1	**< 0.001**
VADS-B					
Aural Oral	6.3 ± 1.0	6.0	5.7 ± 1.1	6.0	**0.018**
Visual Oral	6.6 ± 0.9	7.0	5.9 ± 1.2	6.0	**0.015**
Aural Written	6.7 ± 1.1	6.0	5.6 ± 1.2	5.0	**< 0.001**
Visual Written	7.2 ± 1.2	7.0	6.4 ± 1.5	6.5	**0.010**
Aural Input Score	13.0 ± 1.9	13.0	11.4 ± 2.0	11.0	**< 0.001**
Visual Input Score	13.8 ± 1.7	14.0	12.4 ± 2.4	12.0	**0.005**
Oral Expression Score	12.9 ± 1.7	13.0	11.7 ± 2.1	11.5	**0.004**
Written Expression Score	13.9 ± 1.9	14.0	12.1 ± 2.4	12.0	**< 0.001**
Intrasensory Integration Score	13.5 ± 1.7	14.0	12.2 ± 2.2	12.5	**0.003**
Intersensory Integration Score	13.3 ± 1.8	13.0	11.6 ± 2.1	11.0	**< 0.001**
Total Score	26.8 ± 3.2	27.0	23.7 ± 4.0	24.0	**< 0.001**

Mann–Whitney U test

Significant values are presented in bold characters

Table 4 Comparisons of serum BDNF levels

	Control group ($n=36$)		Case group ($n=54$)		p
	Mean. ± sd/n-%	Median	Mean. ± sd/n-%	Median	
Serum BDNF Level (ng/ml)	12.8 ± 6.4	15.4	10.9 ± 6.9	8.9	**0.044**[c]
Serum BDNF Level (ng/ml) (Male)	12.4 ± 6.9	10.8	8.8 ± 6.2	6.7	**0.037**[a]
Serum BDNF Level (ng/ml) (Female)	11.68 ± 6.9	11	10.22 ± 6.9	10	0.067[a]

[a]Mann–Whitney U test, [c]Two-way ANOVA, BDNF level was selected as an independent factor, and sex and group were administered as fixed factors. Gender had a significant effect on BDNF levels ($F=12.21$; $p=0.008$)

Significant values are presented in bold characters

Comparisons of neuropsychological tests

Stroop test word reading spontaneous correction number and reading time, word color saying wrong number, spontaneous correction number and reading time, box color speaking spontaneous correction number and reading time, Stroop interference and speed factor duration were significantly higher in the COVID-19 group than in

Table 5 Correlation between neuropsychological test scores and serum BDNF levels in the case group

		Serum BDNF level (ng/ml)			
		Female ($n=22$)		Male ($n=14$)	
		r	*p*	*r*	*p*
Stroop Word Reading	Number of correct word	0.060	0.701	**– 0.481**	**0.031**
	Number of wrong word	– 0.061	0.743	0.142	0.442
	Spontaneous correction	– 0.012	0.948	0.028	0.900
	Reading time	– 0.285	0.120	**– 0.555**	**0.001**
Stroop Saying The Word's Color	Number of correct word	0.284	0.121	**0.532**	**0.003**
	Number of wrong word	– 0.284	– 0.121	– 0.072	0.744
	Spontaneous correction	– 0.087	0.640	0.063	0.775
	Saying time	– 0.200	0.282	0.010	0.964
Stroop Saying The Box's Color	Number of correct word	– 0.073	0.695	**– 0.513**	**0.001**
	Number of wrong word	0.073	0.695	0.192	0.481
	Spontaneous correction	– 0.134	0.472	0.028	0.900
	Saying time	– 0.171	0.358	**– 0.491**	**0.003**
Interference		– 0.128	0,494	**– 0.505**	**0.033**
The Speed Factor		– 0.266	0,148	– 0.211	0.333
VADS	Aural Oral	– 0.020	0.196	0.115	0.601
	Visual Oral	0.211	0.255	0.227	0.297
	Aural Written	0.060	0.747	0.176	0.421
	Visual Written	0.029	0.877	0.185	0.399
	Aural Input Score	– 0.056	0.766	0.142	0.517
	Visual Input Score	0.132	0.480	0.201	0.358
	Oral Expression Score	0.132	0.478	0.175	0.424
	Written Expression Score	0.027	0.885	0.214	0.328
	Intrasensory Integration Score	– 0.022	0.907	0.220	0.314
	Intersensory Integration Score	0.120	0.521	0.200	0.360
	Total score	0.030	0.874	0.201	0.358

Spearman Correlation

Significant values are presented in bold characters

the control group ($p < 0.05$). All scores of the VADS-B test were found to be significantly lower in the COVID-19 group than in the control group ($p < 0.05$). Stroop test and VADS-B test data are shown in Table 3.

Comparison of serum BDNF levels

The mean serum BDNF level was selected as an independent factor, and sex and group were administered as fixed factors. BDNF levels were found to be 10.92 ± 6.91 ng/ml in the COVID-19 group and 12.83 ± 6.41 ng/ml in the healthy control group. Gender had a significant effect on BDNF levels ($F = 12.21$; $p = 0.008$). Two-way ANOVA showed that the serum mean BDNF level was significantly higher in the COVID-19 group than in the control group ($F = 12.22$; $p = 0.044$). A comparison of the serum BDNF levels of the two groups is shown in Table 4 (Table 4).

Correlation analysis

There were no significant correlations between neurocognitive tests and serum BDNF levels in female participants in case group. In male participants, there were significant negative correlations between Stroop Word Reading (number of correct word and reading time), Stroop Saying The Word's Color (number of correct word), Stroop Saying The Box's Color (number of correct word and reading time) and speed factor duration and serum BDNF level (Table 5). There were not any correlations between both female and male groups' neurocognitive tests and serum BDNF level in control group (Table 6). There were not any significant correlations between the scores of HDRS, HAMA-14, times passed after COVID-19 and serum

Table 6 Correlation between neuropsychological test scores and serum BDNF levels in control group

		Serum BDNF level			
		Female ($n=31$)		Male ($n=23$)	
		r	p	r	p
Stroop Word Reading	Number of correct word	0.070	0.622	− 0.033	0.801
	Number of wrong word	− 0.071	0.632	− 0.222	0.123
	Spontaneous correction	− 0.036	0.801	− 0.023	0.891
	Reading time	− 0.243	0.083	− 0.255	0.127
Stroop Saying The Word's Color	Number of correct word	0.191	0.167	0.180	0.286
	Number of wrong word	− 0.193	0.168	− 0.180	0.286
	Spontaneous correction	− 0.202	0.152	− 0.283	0.089
	Saying time	− 0.322	0.051	− 0.228	0.175
Stroop Saying The Box's Color	Number of correct word	− 0.061	0.670	0.140	0.407
	Number of wrong word	0.060	0.673	− 0.140	0.407
	Spontaneous correction	− 0.197	0.161	− 0.034	0.840
	Saying time	− 0.125	0.378	− 0.265	0.113
Interference		− 0.288	0.441	− 0.103	0.543
The Speed Factor		− 0.170	0.229	− 0.193	0.253
VADS	Aural Oral	− 0.007	0.959	0.146	0.388
	Visual Oral	0.251	0.073	0.138	0.414
	Aural Written	− 0.021	0.885	0.308	0.064
	Visual Written	− 0.030	0.832	0.285	0.087
	Aural Input Score	− 0.006	0.969	0.273	0.102
	Visual Input Score	0.159	0.259	0.258	0.123
	Oral Expression Score	0.162	0.252	0.137	0.418
	Written Expression Score	0.021	0.885	0.313	0.060
	Intrasensory Integration Score	− 0.009	0.948	0.327	0.058
	Intersensory Integration Score	0.152	0.282	0.260	0.121
	Total score	0.082	0.561	0.288	0.084

Spearman Correlation

BDNF levels (respectively, $r=0.076$, $p=0.637$; $r=0.126$, $p=0.744$; $r=0.214$, $p=0.432$).

Discussion

In the present study, the main findings were as followings: Stroop test word reading spontaneous correction number and reading time, word color saying wrong number, spontaneous correction number and reading time, box color speaking spontaneous correction number and reading time, Stroop interference and speed factor duration were significantly higher in the COVID-19 group than in the control group. All scores of the VADS-B test were found to be significantly lower in the COVID-19 group. The mean serum BDNF levels were found to be 10.9 ± 6.9 ng/ml in the COVID-19 group and 12.8 ± 6.4 ng/ml in the healthy control group. Two-way ANOVA showed that the serum mean BDNF level was significantly lower in the COVID-19 group than in the control group. Gender had a significant effect on BDNF levels ($F=12.21$; $p=0.008$).

Several studies have investigated the effects of COVID-19 infection on cognitive function after recovery. In a previous study, 18 men and 11 women who had experienced COVID-19 were assessed, and it was found that cognitive functions were impaired in the field of selective attention three weeks after the disease [17]. In another study in which 97 patients were included, cognitive functions

were screened 8 months after COVID-19. It was found that 33% of the patients reported impaired attention, and 27% of them reported a decrease in memory [18]. In a study that evaluated the cognitive function of patients who did not need to be hospitalized due to COVID-19, it was shown that there were decreases in attention and short-term memory function compared to healthy controls [19]. The results of the present study are in line with the literature and indicate a decline in cognitive function, especially in attention and short-term memory.

The patients who had mild COVID-19 were evaluated 6 months later in terms of cognitive function, and it was found that cognitive function decreased in these individuals compared to the preepidemic situation [20]. Another study showed that memory, attention, executive functions and language were lower in people who had COVID-19 than in those who had not, and it has been shown that decreased cognitive function was not associated with the severity of the disease [21]. In another study, the cognitive function of people who had COVID-19 was examined 3 months after the infection, and it was reported that one-third of these people had deterioration in cognitive function. However, it was also found that the severity of the disease did not correlate with the deterioration in cognitive function [22]. In a meta-analysis that included 43 studies, it was reported that approximately 20% of people showed cognitive dysfunction for 3 or more months after COVID-19; however, there was no significant association between deterioration of cognitive function and severity of illness [23]. A recent study demonstrated that cognitive dysfunction was more common in people who had severe illness and who needed to stay in the intensive care unit for a longer period of time [24]. Although there are conflicting results about the relationship between the degree of cognitive function and the severity of the disease, our study indicated that cognitive decline can be observed even in young people with mild illness and in people who have had the disease for more than 6 months.

There have been few studies that have investigated the role of serum BDNF and cognitive decline in patients with COVID-19 infection. Azoulay et al., showed that lower serum BDNF levels were found in patients with severe disease, and serum BDNF levels returned to normal over time. They also reported that the serum BDNF levels in males were lower than those of females, and thus, it was interpreted that the serum BDNF level could be a prognostic indicator, especially in male patients [25]. Studies have reported that the more severe course of COVID-19 in men may be related to the higher expression of ACE-2 in men [26–28]. In our study, we found that serum BDNF levels were significantly lower in the COVID-19 group, when a two-way ANCOVA model was applied. Sex was shown to have a significant effect on serum BDNF levels. Higher expression levels of ACE-2 in males may be associated with lower levels of serum BDNF in male patients with COVID-19 infection.

Although we calculated the sample size for the present study, the small sample size can be considered a limitation. The inclusion of only patients who recovered from mild COVID-19 and the exclusion of patients who recovered from severe to moderate COVID-19 might have resulted in false-negative findings, and this issue is another limitation of the present study. Pro-BDNF is the precursor of mature BDNF and has been reported to have different effects on the etiology of major depressive disorder [29]. We could not measure serum pro-BDNF levels, which is another limitation of the present research.

The present study is the first to demonstrate the association between the role of serum BDNF and cognitive decline in patients with COVID-19 infection. Additionally, there is a significant role of male gender in terms of lower BDNF level and cognitive decline. Our results indicated that cognitive decline occurred after recovery and that this decline persisted. Further studies are needed to demonstrate the effects of COVID-19 infection on long-lasting cognitive dysfunction.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University according to the Declaration of Helsinki.

Consent to participate Informed written consent was obtained from all parents and/or care providers of the patients; the participation in the study was voluntary, and the data processed anonymously.

Consent for publication All authors agree with the publication of this paper.

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