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Post-COVID syndrome? COVID-19 survivors suffer from cognitive difficulties, somatic complaints and anxiety

Uğur Eray[1], Basar Ayrıbas[2], Ömer Furkan Çağlar[3], Turgut Hacıoğlu[4], Fatih Medetalibeyoğlu[5]

[1]Kars Harakani State Hospital, Department of Psychiatry, Kars, Turkey
[2]LWL Child and Adolescent Psychiatry, Münster, Germany
[3]Tokat Gaziosmanpaşa University, Department of Psychiatry, Tokat, Turkey
[4]Kafkas University, Department of Psychiatry, Kars, Turkey
[5]Kafkas University, Department of Biomedical Engineering, Kars, Turkey

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ABSTRACT

Aim: Although primarily known as a respiratory system pathology, COVID-19 may cause various systems and cause serious complications including neuropsychiatric problems. These complications may be formulized as post-COVID syndrome. The current study aims to investigate prolonged cognitive, somatic and psychiatric effects of COVID-19.

Material and Method: A total number of 120 COVID-19 survivors were compared with 120 health controls in means of three measures, which are Cognitive Failures Questionnaire (CFQ), Body Sensations Questionnaire (BSQ), Hospital Anxiety and Depression Scale (HADS) to assess cognitive difficulties, body perceptions and anxiety/depression.

Results: Our findings show that COVID-19 survivors have reported significantly more cognitive difficulties, increased body sensations and higher levels of anxiety. The groups did not differ in means of depression scores. Further, the measures were significantly correlated with each other.

Conclusion: This study reveal that COVID-19 survivors suffer from significant cognitive deficits in everyday activities, are significantly more sensitive to various body sensations and have increased anxiety levels. In discordance with the current literature, our findings showed that COVID-19 patients are not more depressed than healthy subjects. In summary, the current study showed that various neuropsychiatric complications may be an important part of prolonged effects of COVID-19.

Keywords: COVID-19, neuropsychiatry, post-COVID syndrome, cognitive deficits

INTRODUCTION

In December 2019 a new severe acute respiratory syndrome, named as SARS-CoV2, has been reported from Wuhan Region of China. Further studies on this new type of viral infection resulted to rename it as Coronavirus Disease 2019 (COVID-19) by World Health Organization (WHO) (1). Further, WHO defined this new infection as a pandemic in March 2020, as the infection spread worldwide in a very short period of time (2). Various studies reported that main route of transmission is virus containing droplets and close contact with an infected person (3).

Although COVID-19 is mostly known as viral infection effecting respiratory system, almost all body systems or organs can be affected by it. Most common symptoms are fever, non-productive cough, dyspnea, headaches, dizziness, fatigue, diarrhea and vomiting (4). Apart from the serious respiratory signs like respiratory distress or even respiratory failure, COVID-19 can cause various complications. Several studies report myocarditis, cardiac arrythmias or acute coroner syndrome related to COVID-19 (5). Further, neurological complications of COVID-19 such as vertigo, headache, altered consciousness, acute ischemic stroke or intracranial hemorrhages has been also reported (6).

Beside the abovementioned complications, some of the recent viral pandemics are also known for their negative neurocognitive consequences. Several studies reported neuropsychiatric complications associated with viral infections like Influenza A (H1N1), SARS or Middle East Respiratory Syndrome (7). For example survivors of SARS has been reported to suffer from both cognitive difficulties like concentration difficulties, memory impairments, insomnia and symptoms of anxiety and depression (8).

Corresponding Author: Uğur Eray, drugureray@gmail.com
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Coronaviruses are widely known as neuro-invasive, neurotropic and neurovirulent type viruses (9). It is known that infection caused by these types of viruses may cause various psychiatric problems in acute or chronic phases (10). Additionally, it has been reported that existence of somatic symptoms like fever, cough, fatigue and gastrointestinal disturbances may exacerbate psychological complications (11)

In case of SARS-Cov-2 viruses, it has been postulated that viruses use ACE receptors a binding site to invade various cell types (12) . More specifically ACE2 receptors are mostly involved in this process. Studies show that apart from respiratory system, ACE2 receptors are widely distributed in central nervous system and SARS-Cov-2 type viruses can reach to the various nervous system cells like neurons, astrocytes and oligodendrocytes through these receptors (8). Another pathophysiologic mechanisms have been also proposed to understand SARS-Cov-2 viruses and their neuropsychiatric complications. One of these mechanisms is knowns as "cytokine storm" theory. According to this theory after binding to ACE-2 receptors, Coronaviruses trigger a cytokine storm characterized by significant increases in Interleukin-1, Interleukin-2 and Tumor Necrosis Factor (13). These increased cytokine levels cause significant cell damage and consequently results with increased vascular permeability and widespread inflammation. These changes may also be evident in Blood Brain Barrier (BBB), as cytokine storm can damage BBB and therefore cause some neuropsychiatric complications like memory impairments and working memory difficulties (14).

Apart from the abovementioned biologic factors, numerous psychological factors were also proposed to understand psychiatric complications of COVID-19. Traumatic experiences like natural catastrophes or diseases may affect the feelings of security or act as a remainder of death (15). In case of COVID-19, factors like uncertainties regarding the course of the pandemic, lack of cure for the disease, overload of information, restricted social and physical activities may be significant factors which may serve as precipitating or causative factors for neuropsychiatric complications (16). In this context, several studies report that both COVID-19 survivors and general population show increased levels of anxiety, depression, fear responses and sleep disturbances (17,18). Relatedly, studies show that almost half of the COVID-19 survivors report emotional disturbances after acute phase of the infection and there is an increased risk to be referred for psychiatric treatment (19). In this regard, several studies also show that both severe and mild COVID-19 infections are associated with neurocognitive deficits (20). For example Gennaro et al. (21) showed that neurocognitive deficits and depression in COVID-19 patients are related to prolonged effect of inflammatory hyperactivation.

In summary, several studies on COVID-19 show that both acute and post-acute period of this disease are associated with various complications and it has been proposed that a possible post-COVID Syndrome is already definable (22). Further, it has also been shown that neurocognitive deficits and psychiatric symptoms are one of the most common symptom clusters associated with post-COVID syndrome (23).

In this current study it was aimed to search the effect of COVID-19 infection in means of cognitive difficulties, perception of body sensations and depression and anxiety by comparing COVID-19 survivors with healthy subjects.

MATERIAL AND METHOD

This case-controlled study was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Ethics approval was applied and obtained from the Kafkas University Ethics Committee (Date: 11.03.2021, Decision No: 80576354-050-99/26).

An online data form including informed consent, sociodemographic info and three questionnaires was generated in Google Docs and participants were asked to fill this form online. A written informed consent was obtained from all participants, both patient group and healthy controls. This study was conducted from March 2021 to May 2021 with a total number of 240 participants, 120 COVID-19 survivors and 120 healthy controls. All participants were over the age of 18. Participants were reached and recruited from patient pool of an University Hospital in Türkiye. Exclusion criteria for patient group were any history of psychiatric or neurological disorders, being illiterate, acute phase of COVID-19 ,ongoing treatment for COVID-19 or receiving treatment in the intensive care unit due to COVID-19. Healthy controls were recruited among the college students and social media platforms. Exclusion criteria for control group were any chronic medical conditions including psychiatric and neurological disorders, being infected with COVID-19 or being vaccinated with any type of COVID-19 vaccines and being illiterate.

Measures

Cognitive Failures Questionnaire (CFQ): Developed by Broadbendt et al. (24), CFQ is a self-report measure to evaluate everyday cognitive functions. CFQ consists of 25 items to measure three dimensions of cognition: perception, memory and motor functions. It has a five-point Likert style and every item can be scored between 0 to 4. Total scores range between 0 – 100 and higher scores indicate greater cognitive difficulties in daily activities. A Turkish validation study of CFQ has been conducted by Ekici et al. (25) and it has been found to be a reliable and valid measure to use in Turkish.

Body sensations questionnaire: Body Sensations Questionnaire (BSQ) is a self-reported measure and consists of 17 items (26). Items of BSQ consist of various bodily sensations and subjects are asked to choose a score to assign how fearful each sensation is. Items can be scored between 1 and 5 points and the total score can be reported. Higher scores on BSQ indicates more fear from somatic sensations. Turkish validation study of BSQ was conducted by Kart et al. (27) and it was reported as a valid and reliable scale in Turkish population.

Hospital anxiety and depression scale (HADS): HADS was developed in 1983 and it is widely used in different clinical or non-clinical settings to evaluate depression and anxiety in somatic disorders (28). It is a self-report measure and consists of 14 items, 7 for anxiety and 7 for depression. It has a four-point Likert structure and each item can be scored between 0 – 3 points. Higher scores indicate higher levels of anxiety and depression. Turkish validation study of HADS was conducted in 1997 and it was reported as a valid and reliable measure (29).

Statistical Analysis

The G* Power software version 3.01 (Franz Faul, Kiel, Germany) was implemented for power analysis to estimate sample size. At a=0.05 significance level, to reveal a medium effect size (d=0.5) with 80% power, participants in each study arm (totally 244 participants) were found to be necessary. The distribution analysis of data was evaluated by Kolmogorov-Smirnov and Shapiro Wilks test. Independent samples t-test was used for normally distributed continuous variables. Mann-Whitney-U test was used as nonparametric test for continuous variables. Categorical variables were analyzed with the Chi-Squared Test. Pearson correlation analysis was used to determine the correlation between the continuous variables. Standard Multiple Regression technique was used to determine the effects of various parameters on cognitive effects of COVID-19. IBM SPSS Statistics 24 (SPSS IBM, Chicago) program was used to analyze. Statistically significance was accepted as p-values below 0.05.

RESULTS

The patient group and health controls did not differ significantly from each other in means of age, sex and years of education as shown in **Table 1**.

The distribution of time period after COVID-19 infection in patient group was as following; 8 (6.7%) patients between 15 days to 1 month, 37 (30.8%) patients between 1-3 month, 64 (53.3%) patients between 3-6 months and 11 (9.2%) patients more than 6 months.

14 (11.7%) of 120 COVID-19 patients were admitted to hospital and 106 (88.3%) of 120 patients were participants who were treated as outpatient.

Table 1. Sociodemographic variables of participants

Parental Measures	Patient Group	Control Group	p value
n	120	120	
Sex [n males/females]	38/82	44/76	0.414 (χ2:0.667)[1]
Age [M (SD)]	33.62 (±11.39)	31.38 (±9.24)	0.962[2]
Years of Education: [M (SD)]	15.45 (±2.67)	15.10 (±3.46)	0.393[2]

1: Chi-square test, 2: independent samples t-test

69 (57.5%) participants form patient group subjectively responded that they suffer from ongoing somatic effects of COVID-19. Similarly, 40 (33.3%) patients have reported that they have still negative psychological effects of COVID-19.

The mean scores of measures from both groups have been found as following; The CFQ scores were 40.29 (±15.48) in the patient group and 36.00 (±15.58) in the control group, BSQ scores were 33.06 (±13.17) in the patient group and 28.01 (±10.09) in the control group HADS-A scores were 9.00 (±4.31) in the patient group and 7.39 (±4.22) in the control group. HADS-D scores were 6.92 (±4.37) in the patient group and 6.45 (±4.41) in the control group. HADS-T scores were 15.93 (±7.76) in the patient group and 13.84 (±7.65) in the control group.

The patient group had significantly higher scores on CFQ (p:0,034), BSQ (p:0,001), HADS-A (p:0,004) and HADS-T (p:0,037), but the groups did not differ in means of depression scores on HADS-D (p:0,404) as shown in **Table 2**. Similarly, a significant positive correlation relationship between scores of measures has been found as shown in **Table 3**.

Table 2. Comparison of measures between parents of patients and healthy controls

Measures	Patient Group	Control Group	p value[1]
n	120	120	
CFQ[M (SD)]	40.29 (±15.48)	36.00 (±15.58)	**0.034**
BSQ[M (SD)]	33.06 (±13.17)	28.01 (±10.09)	**0.001**
HADS-A[M (SD)]	9.00 (±4.31)	7.39 (±4.22)	**0.004**
HADS-D[M (SD)]	6.92 (±4.37)	6.45 (±4.41)	0.404
HADS-T[M (SD)]	15.93 (±7.76)	13.84 (±7.65)	**0.037**

1: independent samples t-test CFQ: Cognitive Failures Questionnaire, BSQ: Body Sensations Questionnaire, HADS-A: Hospital Anxiety and Depression Scale – Anxiety, HADS-D: HADS Depression, HADS-T: HADS Total Score

Table 3. Correlation analyses of measures in patient and control groups and total sample

Total Sample (n:240)					
Measure	**CFQ**	**BSQ**	**HADS-A**	**HADS-D**	**HADS-T**
1. CFQ	1	0.471**	0.533**	0.482**	0.570**
2. BSQ			0.481**	0.362**	0.474**
3. HADSA				0.581**	0.888**
4. HADSD					0.891**
5. HADST					1

CFQ: Cognitive Failures Questionnaire, BSQ: Body Sensations Questionnaire, HADS-A: Hospital Anxiety and Depression Scale – Anxiety, HADS-D: HADS Depression, HADS-T: HADS Total Score * p < .05 (two-tailed). ** p < .01 (two-tailed).

Finally the regression analysis showed that perception of body perceptions, anxiety and depression scores significantly contribute to cognitive impairment, as shown in **Table 4**.

Table 4. Predictive values of BSQ, anxiety and depression scores on CFQ

Number of Subjects: 240			
Predictor	**Beta**	**p**	**r**
BSQ	0.251	**0.000**	0.217
HADS-A	0.275	**0.000**	0.207
HADS-D	0.230	**0.000**	0.185
History of COVID	0.020	0.704	0.020
Fit for model R2=0.378, Adjusted R2=0.368, p <0.00			

CFQ: Cognitive Failures Questionnaire, BSQ: Body Sensations Questionnaire, HADS-A: Hospital Anxiety and Depression Scale – Anxiety, HADS-D: HADS Depression

DISCUSSION

The findings from the current study show that survivors of COVID-19 suffer from cognitive difficulties during everyday practices as measured by CFQ, increased sensitivity to various body sensations as measured by BSQ and increased anxiety as measured by HADS. Moreover, these impairments seem to be correlated to each other.

The neurocognitive deterioration after COVID-19 is a well-known and replicated finding from numerous studies and some authors formulize this situation as "cognitive COVID" (30). Studies show that these cognitive impairments are mostly related to general inflammatory processes and the long-term outcomes of these impairments are largely unknown. Nevertheless, some studies conclude that high frequency of cognitive impairments in COVID-19 survivors deserve special attention and early interventions targeting these impairments should be considered (31). In this regard our findings that cognitive dysfunction was found to be significantly higher in the patient group also replicate this findings, as 33% of our patient sample subjectively reported that, they suffer from psychological consequences of COVID-19, apart from their scores on measures used in the current study. Also the CFQ scores from the current study indicates that COVID-19 survivors suffer from cognitive impairments. This finding should be discussed in light of high anxiety levels of patient group in the current study. Our results show that there is a high correlation between cognitive impairments and anxiety levels and it may be suggested that anxiety can also be a precipitating factor in cognitive difficulties in COVID-19 patients. Moreover our regression analysis model also shows that although BSQ scores, anxiety and depression have separately significant effects on cognitive difficulties, most significant factor among these parameters was anxiety. Further this regression analysis showed that there is no significant effect of COVID-19 itself on cognitive dysfunctions in patients. Therefore it can be postulated that cognitive difficulties seen in COVID-19 survivors are probably through increased anxiety, fear from somatic sensation and depression rather than COVID-19 itself. This relationship is already evident in different medical conditions, as studies show that anxiety levels are correlated with cognitive dysfunctions in inflammatory disorders (32). This finding is also evident in COVID-19, as studies show high anxiety levels in COVID-19 survivors and its relationship between cognitive dysfunction (33,34).

In contrast to increased anxiety levels in COVID-19 survivors compared to healthy controls, it this study these two group did not differ in means of depression scores. This finding is seems to be unusual in the literature, as almost all studies conclude an increased risk of depression in COVID-19 patients or survivors compared to healthy subjects (35). This finding may be caused from different factors like age, sex and disease severity. In contrast to other studies our sample seems to be younger in age and has more females compared to males (22). Furthermore the rate of admitted patients to the hospital due to COVID-19, a strong predictive factor of symptom severity, seems be lower in the current study compared to the literature (22). Therefore it can be interpretated that our patient group might have lower symptom severity compared to similar studies. Another reason of similar depression scores between groups may be the exclusion criteria of the current study, as patients with current psychiatric disorders including mood disorders were excluded from data analysis to neutralize possible confounding effect of depression on cognitive functions. This exclusion may be important, as studies point that history of any psychiatric disorder seems to be associated with worser post-COVID psychological functioning (22).

Another important finding from the current study is the increased BSQ scores in COVID-19 survivors compared to healthy subjects. This finding should be discussed with the another finding from current study which shows that more than half of the COVID-19 survivors subjectively think that they still suffer from one or more somatic symptoms. BSQ is mostly used to predict the fear from bodily perceptions associated with anxiety, somatoform disorders and non-organic pain related disorders (36). Although there has been no other study using BSQ in COVID-19 can be found in the literature, some studies showing increased levels of somatization and health anxiety related to COVID-19 (37,38).

Limitations

One of the main limitations of the current study is the sampling method, as both patient and control groups are reached through online platforms and asked to fill questionnaires online. This may limit the generalizability of our results. Another limitation was the information gathering method. All our questionnaires were self-report

measures, and this type of measures may not be ideally objective. This problem can be more crucial in case of cognitive assessment, and we suggest more objective measures to assess neurocognitive functions for further studies. There was one person over 65 years of age in the patient group and two people in the control group. Although all patients were healthy in terms of dementia on examination, advanced age may have affected our results. Having an additional chronic disease was determined as an exclusion criterion in the healthy control group but not in patient group because of the risk of sampling bias in COVID-19 group. However, not questioning an additional chronic disease which may impair cognitive functions in the patient group may be considers as an another limitations of the current study. Similarly the lack of information on the medications of patients, which can also effect cognitive functions, might have also limit the generalizability of the results.

CONCLUSION

In summary, apart from depression levels, our results seem to be in line with the current literature on neuropsychiatric outcomes of COVID-19. Based on findings from the current study, it may be suggested that COVID-19 survivors suffer from high anxiety, cognitive impairments and more fear from body sensations. Therefore it may be important to screen COVID-19 patients in long term in means of preventive measures and interventions regarding cognitive abilities and psychological functioning.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics approval was applied and obtained from the Kafkas University Ethics Committee (Date: 11.03.2021, Decision No: 80576354-050-99/26).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author 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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