Cognitive effects of COVID-19

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ABSTRACT

Objective: Neurological involvement can be seen in Covid-19 and cognitive functions can be affected negatively. There is not enough study and data about cognitive functions of patients followed with Covid-19 diagnosis. For this reason, the current study aims to examine the cognitive functions of patients diagnosed with Covid-19.

Material and Methods: Patients, who were hospitalized and followed-up with the diagnosis of Covid-19, were selected as consecutive. For evaluating cognitive functions, Montreal Cognitive Assessment (MoCA) test was performed to under 65-year-old participants, Standardized Mini- Mental State Exam (MMSE) test was performed to 65-year-old and older participants and Hospital Anxiety and Depression Scale (HADS) was performed to all participants.

Results: The study has consisted of 32 patients and 35 volunteers. The mean of MMSE scores was found to be lower in the patient group than the control group ($p > 0.05$). The mean of MoCA scores was found to be lower in the patient group than the control group, and it was statistically significant ($p < 0.05$). Also, in the sub-group analyzes that assessed the attention of the MoCA test group, the patient group scores were lower than the control group and it was statistically significant ($p < 0.05$). Hospital anxiety scale scores of the patient group were found to be significantly higher than the control group ($p < 0.05$).

Conclusion: The result of this study is showed the presence of cognitive impairment and increased anxiety in patients with Covid-19 who had no previous cognitive deficit. Therefore, it is important to evaluate the patients with Covid-19 in terms of mood and cognition in detail.

Keywords: Covid-19; Cognition; Attention; Anxiety; Depression

INTRODUCTION

Covid-19, which is the member of the Coronaviridea family, was first seen in December 2019 in China. Covid-19 spread rapidly all over the world and was declared as a pandemic by the World Health Organization (WHO) in March 2020 (1). Coronavirus is an infection that can lead a multiple system involvement in animals (2). In the first period of the disease, respiratory tract involvement was mostly dwelled on as clinical findings, in time, it was understood that the disease did not only affect the respiratory tract, but also neurological signs and symptoms were present in 30-35% of patients (1, 3). It has been reported increased stroke risk and neurological symptoms such as headache, impaired consciousness, myalgia, epileptic seizures, rhabdomyolyses, anosmia, and Guillain-Barre Syndrome (1, 4, 5). Recent studies show that the disease is particularly effective on ACE2 receptors, and these receptors are also found in the Central Nervous System (CNS) and skeletal muscles (6). Direct invasion of CNS, the virus entering the CSF circulation and a possible immunosuppression can cause the neurological findings. Also, non-immunologically; it is thought to be micro and macrovascular thrombosis contingent on hypotension and hypoxia may cause neurological damage together with septic encephalopathy (5). Patients who are followed- up with the diagnosis of Covid-19, have been seen CNS involvement with these mechanisms. CNS involvement may affect the cognitive functions in a negative way and for this reason, it is considered to be a risk factor in terms of cognitive functions impairment. There are not enough studies and data related with cognitive functions of patients with diagnosed Covid-19. Therefore, this study aimed to investigate the cognitive functions of patients who were diagnosed with Covid-19.

MATERIAL and METHODS

Participants

Patients, who were hospitalized and followed-up with the diagnosis of Covid-19 were selected as consecutive. This study included 32 patients over the age of 18 and 35 volunteers who were hospitalized with a diagnosis other than Covid-19, similar sex and age. All participants were literate. Demographic data, systemic disorders, medications used, and existing neurological examinations of the patients were recorded. Patients with a history of dementia, a disease that could prevent compliance with neuropsychological tests such as malignancy, severe cardiac disease, severe hearing loss and visual impairment, and a history of psychoactive drug use were excluded from the study.

Data Collection

For evaluating cognitive functions, MoCA scale (7) was performed to under 65-year- old participants, MMSE scale (8) was performed to 65-year-old and older participants and HADS (9) was performed to all participants.

Montreal Cognitive Assessment Test (MoCA): This scale was developed as a speed screening test to determine mild cognitive impairment. Eight different cognitive domain, which consists of short-term memory, visuospatial abilities, multiple aspects of executive functions, attention and concentration, language, abstract reasoning, and orientation, are evaluated with this scale. MoCA scores range between 0 and 30 (7).

Standardized Mini-Mental State Exam Test (MMSE): This test is a widely used test of cognitive function among the elderly; it includes tests of orientation, attention, memory, language and visual-spatial skills. MMSE scores range between 0 and 30 (10).

Hospital Anxiety and Depression Scale (HADS): HADS is a questionnaire widely used for detecting anxiety and depressive disorders in patients with physical illness. It is a feedback scale, and it consists of 14 items, seven of which relate to anxiety symptoms and seven to depressive symptoms. The scores for anxiety and depression can therefore vary from 0 to 21, depending on the presence and severity of the symptoms. Each item was answered by the patient on a 4-point Likert-scale and scored from 0 to 3. Depression and anxiety questions are scored separately. A score between 8 and 10 indicates the presence of the symptomology, but to a moderate degree, a score greater than or equal to 11 indicates a significant number of symptoms of anxiety or depression (9).

The relationship between Covid-19 positivity and cognitive test scores was evaluated considering other possible factors that may affect the cognitive performance of patients as well. This study was approved by the Ministry of Health (Protocol No: 2020-05-16T03-13-40) and the University of Health Science, Gülhane School of Medicine Ethic Committee (09.06.2020/2020-229). Before the study, the informed consent form was taken from all participants. The study was performed in accordance with the principles of Helsinki Declaration.

Statistical analysis: For statistical analysis, SPSS 22.0 was used. Descriptive statistics were used for demographic data. Qualitative variables were indicated with frequency and numerical variables were summarized by mean ± standard deviation. Between group comparisons Independent t- test was used, and p<0.05 was accepted as statistically significant.

RESULTS

This study was conducted on 32 patients (18 male + 14 female) and 35 volunteers (20 male + 15 female). The lowest patient age was 23, and the highest patient age was 85. The mean age of the patients was 51.12 ± 17.52. In control group, the lowest age was 18, and the highest age was 89. The mean age of the control group was 51.11±17.07. There was no statistically significant difference between patient and control groups in terms of age and sex (p>0.05). The number of patients over 65 years old was 9 in the patient group and 10 in the control group. The mean age of the patient group over 65 years old was 69.88±6.21 and the mean age of the control group was 70.70±7.60. There was no statistically significant difference between patient and control groups over 65 years old in terms of age (p>0.05). The number of patients under 65 years old was 23 in the patient group and 25 in the control group. The mean age of patient group under 65 years old was 42.39±14.00 and the mean age of the control group was 43.28±12.95. There was no statistically significant difference between patient and control groups under 65 years old in terms of age (p>0.05).

MMSE scores were compared between patients and the control group over 65 years old. The mean scores were 22.44±3.28 and 23.00±2.90, respectively. MMSE scores were found to be significantly lower in patients than the controls, but it was not statistically significant (p>0.05). In the subgroup analyses (subtracting 7 in series) that assessed the attention of the MMSE test group, the patient group scores (3.00±1.72) were lower than the control group (3.40±1.34), but it was not statistically significant as well (p> 0.05).

MoCA scores were compared between patients and the control group under 65 years old. The mean scores were 23.08±3.02 and 24.28±2.05, respectively. MoCA scores were found to be significantly lower in patients than the controls, and it was statistically significant (p<0.05). In the subgroup analyzes (counting forward and backward, wakefulness, subtracting 7 in series) that assessed the attention of the MoCA test group, the patient group scores (4.00 ± 1.0) were found to be lower than the control group (3.40 ± 1.34), and it was statistically significant (p<0.05).

Hospital depression scale scores were compared between patients and the control group. The mean scores were 7.78±2.73 and 8.45±3.02, respectively. Hospital depression scale scores were found to be significantly lower in patients than the controls, but it was not statistically significant (p>0.05). The number of patients with a hospital depression scale score equal to 8 and above was 20 (62.5%), the number of patients with a hospital depression scale score equal to 11 and above was 5 (15.6%). The number of controls with a hospital depression scale score equal to 8 and above was 21 (60.0%), the number of controls with a hospital depression scale score equal to 11 and above was 7 (20.0%).

Hospital anxiety scale scores were compared between patients and the control group. The hospital anxiety scale scores of the patient group (8.90±2.11) were found to be significantly higher than the control group (4.94±2.14), and it was statistically significant (p<0.05).

The number of patients with a hospital anxiety score equal to 8 and above was 24 (75%), the number of patients with a hospital anxiety score equal to 11 and above was 8 (25%). The number of controls with a hospital anxiety score equal to 8 and above was 5 (14.2%), the number of controls with a hospital anxiety score equal to 11 and above was 2 (5.71%) (**Table 1**).

Table 1: Cognitive findings of patient and control group

Variables	Patient Group (mean±sd)	Control Group (mean±sd)	P value
MMSE	22.44±3.28	23.00±2.90	0.70
MMSE/Attention	3.00±1.72	3.40±1.34	0.50
MoCA	23.08±3.02	24.28±2.05	**0.02**
MoCA/ Attention	4.00±1.00	4.60±0.76	**0.02**
HDS	7.78±2.73	8.45±3.02	0.34
HAS	8.90±2.11	4.94±2.14	**0.00**

Sd: Standard deviation; MMSE: Mini-Mental State Exam; MoCA: Montreal Cognitive Assessment; HDS: Hospital Depression Scale; HAS: Hospital Anxiety Scale

DISCUSSION

Neurological findings are also detected in patients with the diagnosis of Covid-19. One of these findings is the impairments in cognitive functions. In this study, it was evaluated the cognitive functions of patients with Covid-19. For assess cognitive functions, MoCA scale was performed to under 65-year-old participants, MMSE scale was performed to 65-year-old and older participants and HADS was performed to all participants. As a result of the study, MMSE scores were found to be significantly lower in patients than the controls, but it was not statistically significant. In the subgroup analyses (subtracting 7 in series) that assessed the attention of the MMSE test group, the patient group scores were lower than the control group, but it was not statistically significant as well. MoCA scores were found to be significantly lower in the patient group than the control group, and it was statistically significant. In the subgroup analyses (counting forward and backward, wakefulness, subtracting 7 in series) that assessed the attention of the MoCA test group, the patient group scores were found to be lower than the control group, and it was statistically significant. Hospital depression scale scores were found to be significantly lower in patients than the controls, but it was not statistically significant. Also, the hospital anxiety scale scores of the patient group were found to be significantly higher than the control group and it was statistically significant.

Neurological involvement in Covid-19 infection was reported in previous studies (1). Headache was the most commonly seen neurological symptom in this disease. Dizziness, impaired consciousness, anosmia, acute cerebrovascular disorders, ataxia, epileptic seizures and myalgia were reported as other findings apart from the headache (3, 11-14). In one study which was conducted by Li et al. (2020), 221 patients with diagnosed Covid-19 were evaluated retrospectively. As a result of the study, acute ischemic stroke was observed at 5%, cerebral vein thrombosis and cerebral bleeding were found at 0.5% (15). Also, signs of skeletal-muscle damage and peripheral nervous system findings such as taste impairment, anosmia, visual defect and neuralgia can be seen (16).

Hypoxia, multiple organ failure, metabolic and electrolyte imbalances were present in patients with diagnosed Covid-19. It has been known that mental disorders such as changes in consciousness depend on both these situations and applied treatment (17). In the study which was carried out by Mao et al. (2019) 40% of patients have headaches and encephalopathy (11). Also, changes in consciousness with encephalopathy were reported in patients with the diagnosis of Covid-19 (17, 18). Encephalopathy may be the initial symptom of the diagnosis of Covid-19 as well as a risk factor for cognitive impairment in the long term.

Since there is not enough experimental data with Covid-19 yet, the transition of this virus to CNS and possible pathological mechanisms are thought to be similar other corona viruses such as SARS and MERS viruses (19). ACE2 receptors, the primary target of the virus in the respiratory epithelium, are also found in glial cells in the brain and spinal neurons. It is thought that the virus passes from the olfactory epithelium to the brain via retrograde neural pathway or the hematogenous way. In addition, at the viremia stage of the disease, it can reach the brain directly depending on the impaired blood-brain barrier (18). A presence of immunosuppression is another mechanism to clarify the reaching of Covid-19 to CNS. The lower counts of lymphocytes in Covid-19 patients with CNS symptoms support to this hypothesis. Similarly, high D-dimer levels in severe patients may confirm the tendency to pass cerebrovascular disease (19).

In this study, as a result of subgroup analyses of MMSE and MoCA, frontal lobe functions such as attention, selective attention, information processing speed were found to be slightly low in the patient group. High anxiety levels of patients may affect attention, and it can be a causal factor for poor performance in this area. Also, MMSE and MoCA scores were found to be compatible with age and depression levels.

Cognitive damage, in which attention is affected, can generate a predictive condition for dementia that will develop in the future.

It is estimated that depression and anxiety related with Covid-19 are more common in both patients with diagnosis of Covid-19 and healthy people (20). At the beginning of the pandemic, in a one multicenter study, 1210 participants without Covid-19 were evaluated with online questionnaire and as a result of the study anxiety was found to be 28.8% and depression was 16.5% in the mid-severe level (21). Similarly, in another study, which was used HADS scale and conducted on healthy individuals in the first months of the pandemic, the rate of depression associated with Covid-19 in the general population was reported to be 23.6%, and the anxiety rate to 45.1% (22). Also, it was found that Covid-19 has increased the psychiatric symptoms such as depression, anxiety and anger and decreased the quality of life in the general population (23). At the beginning of the pandemic, the increase of depression and anxiety in the general population can be explained with a new and also potentially deadly virus. As a matter of the fact, in one study which was conducted on 114 patients with Covid-19 at the beginning of their treatment, it was found that 44.7% of the patients received at least 1 point from the general anxiety disorder questionnaire and 10.5% at least 3 points (24). This may be related to keeping patients in social isolation during their treatment in the hospital, the risk of being stigmatize, fear of the disease and anger. Unlike the number of few studies in the literature, our study results show less anxiety rates. This can be explained by the fact that our research was conducted in the later months of the pandemic. The better knowledge of the infection, the understanding that the patients can be treated, and the increase in the number of recovered cases, may have resulted in a positive effect on the anxiety of individuals.

This study had several limitations. Firstly, patients diagnosed with Covid-19 were evaluated in terms of cognitive and psychiatric while the active infection process is ongoing in a hospital. Secondly, although it was learned verbally from the patients that there was no cognitive damage before infection, this information could not be confirmed with objective tests. Also, a small number of participants is another limitation.

CONCLUSION

In conclusion, our study shows the presence of cognitive impairment, especially in the attention sub-area, and increased anxiety in patients with the diagnosis of Covid-19. It is not yet known whether having a Covid-19 infection is a risk factor for developing dementia in the future or not. Therefore, it is important to evaluate the patients with Covid-19 in terms of mood and cognitive in detail in both acute and chronic periods, also treatment should be planned according to the test results if required. We think this study is considered to be important in terms of evaluating the cognition and mood changes in patients with Covid-19 without any cognitive disorder before. Also, in the future, randomized, double-blind, placebo-controlled, multi-centered and long-term studies are needed to clarify the effect of Covid-19 infection on cognitive functions.

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