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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Pattern of Cognitive Deficits in Patients with Post Coronavirus Disease-2019

Koronavirüs Hastalığı-2019 Sonrası Hastalardaki Bilişsel Bozukluk Paternleri

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Abstract

Objectives: Coronavirus disease-2019 (COVID-19) is a viral disease that has caused a worldwide pandemic. Some symptoms may persist for weeks or months following the disease. One of the common symptoms is cognitive deficits. More than one theory is trying to determine how COVID-19 can affect the brain, specifically, the areas affected and the degree to which they are affected, which may lead to new information about the involvement of the mechanisms of the brain. We aimed to determine the affected localizations of the brain and their rates of involvement with neuropsychological tests.

Materials and Methods: Eighteen patients [5 female (F)/13 male (M); 41.5 (34-50) years] with definite COVID-19, who presented to the neurology outpatient clinic with memory problems, and 15 healthy controls (7 F/8 M; 40.3 (27-49) years) were included in the study. Oktem verbal memory processes test, Stroop test, Wechsler memory scale-revised (WMS-R) forward and reverse number range test, visual-spatial functions with simple shape copying tests, and Beck depression test were performed.

Results: A statistically significant difference was found in total learning scores of the Oktem verbal memory processes test, Stroop test parts 1, 4, 5 in long COVID patients and the controls ($p \leq 0.01$, $p \leq 0.01$, $p=0.02$, $p \leq 0.01$). There was no significant difference in the immediate learning of the Oktem verbal memory processes test, WMS-R, visual-spatial functions with simple-shape copying tests and Beck depression test in the control and patient groups ($p=0.18$ $p=0.42$ $p=0.26$, $p=0.10$).

Conclusion: Our study suggests that memory-related findings in patients with COVID-19 are the result of mainly hippocampal involvement and frontal involvement is added to the picture in some of these patients.

Key Words: COVID-19, Stroop Test, Oktem Verbal Memory Processes Test, Cognitive Deficits

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) dünya çapında pandemiye yol açan virütik bir hastalıktır. Hastalığı takiben haftalarca veya aylarca bazı semptomlar devam edebilmektedir. Sık görülen semptomlardan birisi de bilişsel bozukluktur. COVID-19'un beyni nasıl etkileyebileceği birden fazla teoriyle ortaya konulmaya çalışılmaktadır. Hangi alanların etkilendiği ve etkilenme dereceleri beynin tutulum mekanizmaları hakkında yeni bilgilere işaret edebilir. Bu nedenle biz bu çalışmada nöropsikolojik testlerle beynin etkilenen lokalizasyonlarını ve etkilenme derecelerini saptamayı amaçladık.

Gereç ve Yöntem: Kesin COVID-19 geçiren, unutkanlık şikayeti ile nöroloji polikliniğine başvuran 18 hasta [5 kadın (K)/13 erkek (E); 41,5 (34-50) yaş] ve 15 sağlıklı kontrol [7 K/8 E; 40,3 (27-49) yaş] çalışmaya alındı. Öktem sözel bellek süreçleri testi, Stroop testi, sayı erimi testleri, görsel mekansal fonksiyonlar testleri, Beck depresyon testi uygulandı.

Bulgular: Uzun COVID hastaları ve kontrol grubu karşılaştırıldığında Öktem sözel bellek süreçleri testinde total hafıza skorunda, Stroop testinde 1, 4, 5 bölümlerinde istatistiksel olarak anlamlı farklılık saptandı ($p \leq 0,01$, $p \leq 0,01$, $p=0,02$, $p \leq 0,01$). Öktem sözel bellek süreçleri testinde anlık hafıza bölümünde, sayı erimi testlerinde, görsel mekansal fonksiyonlar testlerinde, Beck depresyon testinde hasta ve kontrol grubu karşılaştırıldığında istatistiksel olarak anlamlı bir farklılık bulunmadı ($p=0,18$ $p=0,42$ $p=0,26$, $p=0,10$).

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Sonuç: Bizim çalışmamız COVID-19 geçiren hastalarda hafıza ile ilgili bulguların ağırlıklı olarak hipokampal tutulumu işaret ettiğini, bir bölümünde tabloya frontal tutulumun eklendiğini göstermektedir.

Anahtar Kelimeler: COVID-19, Stroop Test, Öktem Sözel Bellek Süreçleri Testi, Bilişsel Bozukluk

Introduction

Coronavirus disease-2019 (COVID-19) is a viral disease that caused a worldwide pandemic. It was first detected in Wuhan, China at the end of 2019, and quickly spread all over the world. According to the definition of the World Health Organization, the disease is called COVID-19. The virus causing the disease is severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a positive, single-stranded RNA virus, causing SARS (1). COVID-19 was initially considered a respiratory disease, but it is now known to directly affect not only the lungs, but also the heart, vascular, digestive and nervous system (2). Neurological findings are common, and the underlying pathophysiology is complex. Studies suggest that the effect of COVID-19 on the brain may take a variety of forms, such as directly through infection, as an immune response, or through secondary mechanisms, such as hypoxia due to respiratory failure (3). Studies have suggested that the direct invasion of the central nervous system by SARS-CoV-2 can occur in two ways. The first occurs through axonal transport in the olfactory nerve directly from the nose, resulting in infection of the olfactory cortex and other structures in the temporal lobe and brain stem. The second mode involves viral transmission that occurs by a hematogenous route as a result of the disruption of the blood brain barrier (4,5). SARS-CoV-2 binds to the enzymatic area of the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is quite common in organisms, as it is found on the surface of neurons and alveolar, intestinal epithelial, renal endothelial, and neuroepithelial cells. SARS-CoV-2 attacks the organism by attaching itself to ACE2 with spike proteins, resulting in neuroinvasion when its RNA enters the healthy cell, after which the virus begins to reproduce (6). Another mechanism is the immune response. In electroencephalogram recording in a case of COVID-19-associated encephalopathy, a widespread general deceleration activity in the frontal regions and a scan performed by 8F-fluorodeoxyglucose-positron emission tomography also demonstrated diffuse frontal lobe hypometabolism (7). However, the high cytokine levels that were shown to be devoid of neuroinvasion upon the advent of SARS-CoV-2, after the polymerase chain reaction test was found negative in the cerebrospinal fluid (CSF), suggested a possible underlying cytokine-mediated inflammatory process (8). At the same time, a high CSF/serum interleukin-6 (IL-6) ratio was detected in the patient, suggesting that this may lead to glutamate neurotoxicity by increasing neuroinflammatory mediators (9).

Secondary mechanisms are hypoxia due to respiratory failure, and abnormal blood clotting. Thrombotic complications and coagulopathy are associated with viral binding to ACE2 receptors in blood vessel endothelium (10).

Approximately 15-25% of COVID-19 patients experience neurological symptoms, such as headache, confusion, delirium, impaired consciousness, seizures and paralysis (11). In addition, some symptoms may persist for weeks or months following the disease. The underlying pathophysiology of this condition, called long COVID, remains unclear. One of the most frequently complained findings of long COVID is cognitive deficits (12). We aimed to clarify the mechanisms that cause cognitive deficits by determining the degree and localization

Materials and Methods

Eighteen patients with definite COVID-19 who presented to the neurology outpatient clinic with memory problems [5 female (F)/13 male (M); 41.5 (34-50) years] and 15 healthy controls [7 F/8 M; 40.3 (27-49) years] with more than 8 years of education were included in the study. Patients who tested positive for COVID-19 were included in the study after 3-4 months past. Study exclusion criteria included those with a history of neurological and psychiatric diseases, those who received intensive care treatment during COVID-19, and those with acute depression according to the Beck Depression scale.

The following neuropsychogenic tests were applied to detect the mental impairment caused by COVID-19:

Öktem verbal memory processes test (13): Fifteen-word lists are read to the case at one-second intervals. The subject is asked to repeat the words he/she remembers. The score of the case is entered in the rightmost score part. The case does not have a certain duration in the test and is not expected to be repeated in the order of the test material. However, the words that the subject said, in the order they were said, are numbered on the test paper. The goal is to measure how semantically similar words are processed. In the test, this 15-word list is read 10 times. However, if the subject remembers all 15 words, that is, if the memory performance reaches the goal, the words are read once again. If the subject says the 15 words again correctly, full points are considered received despite previous attempts and the test is considered completed.

Stroop test (14): As part of the test, four different cards containing a word or color are shown to the subject in order, and the subject is asked to read the word or color on the card. During the card reading, time to complete the performance of

the case is kept, as well as the mistakes and corrections made by the case. This data are recorded on the score sheet.

Wechsler memory scale-revised (WMS-R) forward and reverse number range test (15): For each case, the numbers from 1-9 are pronounced in a predetermined and mixed order, and these numbers are expected to be repeated by the patient in the same order. This is called the forward number range, and it can be up to a series. An important point during this test is to read the sequences at a rate of one number per second. If the sequences are read slower or faster than this speed, the subject may develop strategies other than attention skills. In the backward range, the subject is expected to say the sequence read starting from the last number and proceeding to the beginning. Also, with this test, a three-number string can be used and increased by one as the subject succeeds, up to a seven-number sequence.

Visual-spatial functions with simple shape copying tests: This is a subtest of the Addenbrooke Cognitive Assessment test (16). Nested shapes, cube drawing and clock drawing tests are applied.

The study was approved by the Local Ethics Committee University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt of Training and Research Hospital (date: 2021-04-05, decision no: 108/16). All investigators confirmed that the ethical standards as described in the Declaration of Helsinki were followed. Written informed consent was obtained from the enrolled subjects.

Statistical Analysis

Data were evaluated using the Statistical Package for the Social Sciences ver. 22 statistics programme (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to verify whether our data were normally distributed or not. Continuous variables were non-normally distributed. Data were expressed as median (minimum-maximum). For group comparison, Mann-Whitney's U test was applied, with significance levels accepted as $p<0.05$.

Results

In this study, immediate learning (5.8 vs 6.4) and total learning scores (99.8 vs 133.2) were determined in long COVID patients and the controls. There was a statistically significant decrease in the total learning scores ($p\leq0.01$). In some parts of the Stroop test, elongation was observed in long COVID patients compared to the controls. The most significant elongations were detected at the first (9.9 vs 6.8), fourth (21.7 vs 16.1) and fifth (30.5 vs 26.3) stages ($p\leq0.01$, $p=0.02$, $p\leq0.01$). At the end of the WMS-R forward and reverse number range test (10.8 vs 12.2) and visual-spatial functions with simple-shape copying tests (7.6 vs 7.8), we found out that there isn't any significant relation between the patients and the control groups ($p=0.42$, $p=0.26$)

When the Beck depression test scores were compared between the patient and controls (15.4 vs.13.4), there had no statistically significant difference, and it was found to be consistent with mild mood disturbance (Table 1).

Discussion

We applied the Öktem Verbal Memory Processes test, Stroop test, Digit Range tests, and Visual-Spatial Functions tests to our patients to enlighten the location and mechanism of cognitive impairment.

The most impaired test in our subjecst was the Öktem Verbal Memory Processes test. This test is sensitive to left hemisphere and hippocampal functions and evaluates information-processing practices related to verbal material (verbal learning, short-term

Table 1: Neuropsychometric test results of patients with COVID-19 and control groups

	Patient	Control	p-value
Age	41.5 (34-50)	40.3 (27-49)	0.81
Gender F/M	5/13	7/8	
Immediate learning*	5.8 (4-7)	6.4(5-8)	0.18
Total learning*	99.8 (86-115)	133.2 (116-144)	p≤0.01
Stroop part 1	9.9 (7-12)	6.8 (6-8)	p≤0.01
Stroop part 2	11.4 (6-18)	8.7 (7-11)	0.07
Stroop part 3	1.2 (8-22)	12 (10-14)	0.12
Stroop part 4	21.7 (10-32)	16.1 (10-23)	0.02
Stroop part 5	30.5 (20-40)	26 (14-38)	p≤0.01
WMS-R**	10.8 (2-19)	12.2 (5-19)	0.42
Visual-spatial***	7.6 (6-8)	7.8 (7-8)	0.26
Beck depression	15.4 (9-21)	13.4 (6-19)	0.10

*Öktem verbal memory processes test, **Wechsler memory scale-revised, ***Visual-spatial functions with simple shape copying tests. $p<0.05$, F/M: Female/Male, COVID:19: Coronavirus disease-2019, WMSR: Wechsler memory scale-revised, F/M: Female/Male

and long-term memory based on free recall, back-disruptive effect, and recognition type recall). The neurocognitive sequelae of COVID-19 can include a wide variety of cognitive and neurobehavioural symptoms. The hippocampus, one of the vital anatomical structures involved in many cognitive processes, is the anatomical location most affected by viral encephalopathies (herpes simplex virus, human immunodeficiency virus, etc.). Hippocampal involvement is thought to be triggered directly by viral endothelial activation and disruption of the blood-brain barrier. Hippocampal pathology often leads to significant memory impairment, with consequences for severe long-term cognitive impairment, in general (17).

We also found impairment in the Stroop test in our patients. The Stroop test evaluates the anterior cingulate cortex in the frontal lobe which is responsible for concentration and selective attention, response inhibition, resistance to interference and information processing speed. In the Stroop test, especially in the fourth and fifth stages of the test, the ability to change the perceptual pattern in line with changing demands and under a "destructive effect" is measured. Therefore, the ability to suppress a habitual behavioural pattern and perform an unusual behaviour is measured, in our study, the most prolonged time was part 4.5 (18). It was also found that 55% of the microstructural changes in the central nervous system occurred after infection in COVID-19 patients, and one-third of these changes were in the frontal lobe. Serum and CSF cytokine levels are recommended as useful biomarkers in the early detection and follow-up of frontal involvement (19). It is important to make this diagnosis because clinicians state that immunomodulatory therapies and IL/IL receptor antagonists may be effective in treatment, as the dominant frontal lobe involvement is the result of a cytokine-mediated hyperinflammatory process (20).

The other test applied to our patients was the number range tests (number range from reverse and flat), which measures attention and alertness, the reticular activator system and diffuse projection system of the thalamus. The skill of "simple attention" can also be thought of as immediate memory or very short-term memory. Therefore, this test can also be called "attention span." There was no significant difference in the Number Range tests in the patient and controls. In a study conducted to investigate the presence of microstructural changes in the central nervous system, resulted with a decrease in hippocampal volume with gray matter volumes measurements, and a stability in thalamus volume (21). As a result of the measurements, it supports our study.

For the visual-spatial functions test, used to evaluate the visual-spatial functions and executive function performances of the case, we applied the nested shapes, cube drawing and clock drawing test, which are the subtests of the Addenbrooke Cognitive Assessment test. We did not detect any significant influence. The Beck depression tests were compatible with mild mental distress. We think that this may be the result of living with the COVID-19 epidemic for more than a year.

Study Limitations

This study has some limitations. Only 18 patients were included. A larger study size would have been more effective to assess mental involvement. Neuropsychological assessment was performed only once three months after the illness passed. Lack of follow-up of the disease is also one of our limitations.

Conclusion

In summary, multiple, different mechanisms may cause the pathology of the cognitive impairment associated with COVID-19. These mechanisms are thought to be axonal invasion of the brain, viral passage through the blood-brain barrier, ischemic cerebrovascular accidents associated with hypercoagulation, hypoxia, cytokine storm, and demyelination due to immune response. However, there may be other mechanisms that have not yet been identified. Our study suggests that memory-related findings in patients with COVID-19 are the result of mainly hippocampal involvement and frontal involvement is added to the picture in some of these patients. As COVID-19 is a new disease, it will take months or even years to characterise the precise nature, extent, and temporal extent of the long-term neurocognitive sequelae. We hope this review can aid future research, diagnosis and treatment of cognitive impairments caused by COVID-19

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (2021-04-05 108/16).

Informed Consent: Written informed consent was obtained from subject who participated in this study.

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Authorship Contributions

Surgical and Medical Practices: N.G.Y, A.C.Ü., Concept: A.C.Ü., Design: N.G.Y., Data Collection or Processing: A.C.Ü., Analysis or Interpretation: N.G.Y, A.C.Ü., Literature Search: N.G.Y, A.C.Ü., Writing: N.G.Y, A.C.Ü.

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