ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Evaluation of Neurologic Symptoms in Patients with Polymerase Chain Reaction-positive COVID-19 and Viral Pneumonia

COVID-19 Polimeraz Zincir Reaksiyonu-pozitif ve Viral Pnömonili Hastalarda Nörolojik Semptomların Değerlendirilmesi

Meltem Karacan Gölen[1], Dilek Yılmaz Okuyan[1]

[1] Department of Neurology Konya State Hospital, Konya, Turkey.

ABSTRACT

Objective: The most frequent symptoms affecting the respiratory system in COVID-19 are fever, dry cough, sore throat, and dyspnea. It has been shown that infections due to COVID-19 disease are not always limited to the respiratory tract, there may also be neurologic involvement, which may occur as a result of the spread of the virus to the central nervous system through various mechanisms. Neurologic involvements include headache, dizziness, seizures, encephalitis, stroke, neuromuscular disorders, and peripheral nervous system involvement.

Method: In this study, neurologic findings,laboratory parameters and other characteristics of 179 patients with COVID-19 pneumonia were evaluated retrospectively.

Results: Headache, dizziness, altered consciousness, myalgia, loss of smell, and taste disturbance were observed in 101/179 (56.4%), 33/179 (18.4%), 20/179 (11.2%), 80/179 (44.6%), 62/179 (34.6%), and 52/179 (29%) patients, respectively. Acute ischemic cerebrovascular disease was observed in 5/179 patients (2.8%) and hemorrhagic cerebrovascular disease was observed in one patient (0.6%). Lymphopenia was observed in 51% and thrombocytopenia was detected in 25.4%. Increased C-reactive protein, ferritin level, creatine kinase, lactate dehydrogenase, and D-dimer levels were observed in 89%, 27%, 17%, 20%, and 34% of the patients, respectively.We found a significant relationship between myalgia and increased CK levels (p = 0.001).

Conclusion: Neurologic symptoms can be the first and only symptom of COVID-19. It is thought that the variety of complications that may develop, the relationship of COVID-19 with neurologic diseases, and disease management will become more understandable with future studies conducted with a multidisciplinary approach.

Keywords: SARS-CoV-2, COVID-19, pandemic, neurologic symptoms and signs

ÖZ

Giriş: Covid-19 hastalarında sıklıkla, ateş ve kuru öksürük, boğaz ağrısı, dispne gibi respiratuar sistemi etkileyen klinik bulgulara rastlanır. COVID-19 hastalığına bağlı enfeksiyonların her zaman solunum yollarına sınırlı kalmadığı ve nörolojik tutulumun da olabileceği gösterilmiştir. Çeşitli mekanizmalarla virüsün santral sinir sistemine yayılım sonucunda oluşabilecek nörolojik tablolar icerisinde; baş ağrısı, baş dönmesi, nöbet, ensefalit, inme ve nöromuskuler bozukluklar, periferik sinir sistemi tutulumları yer almaktadır.

Yöntem: Bu çalışmada COVID-19 pnömonisi olan 179 hastanın eşlik eden nörolojik bulgu, muayene özellikleri ve laboratuar parametreleri retrospektif olarak değerlendirildi.

Bulgular: Çalışmada hastaların 101'inde (%56,4) baş ağrısı, 33'ünde (%18,4) dizziness, 20'sinde (%11,2) bilinç değişikliği, 106'sında (%59,9) miyalji, 62'sinde (%34,6) koku kaybı tespit edilirken, 52 'sinde tat alma bozukluğu(%29) gözlenmiştir. Akut iskemik serebrovasküler hastalık 5 hastada (% 2,8), hemorajik serebrovasküler hastalık ise 1 hastada(% 0,6)gözlenmiştir. Hastaların laboratuar parametrelerini değerlendirdiğimizde lenfopeni % 51'inde, trombosit değerinde değişiklik ise %31'inde tespit edildi. Akut faz reaktanlarından C-reaktif protein (CRP) artışı % 89'unda, ferritin düzeyinde artış ise %27'sinde gözlendi. Hastaların %17 'sinde kreatin kinaz (CK) düzeyinde, %20 sinde ise laktat dehiderogenaz (LDH) düzeyinde %34'ünde de D-dimer artışı izlendi. Miyalji olan hastalarda CK seviyelerinde istatiksel anlamlı artış gözlendi.(p = 0.001).

Sonuç: COVID-19 enfeksiyonuna bağlı klinik tablonun tek bir nörolojik belirti veya bulgu ile de prezente olabileceği akılda tutulmalıdır. Multidisipliner yaklaşımla yapılacak yeni çalışmalarla gelişebilecek komplikasyon çeşitliliğinin, nörolojik hastalıklarla ilişkisinin ve hastalık yönetiminin daha anlaşılır hale geleceği düşünülmektedir.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, pandemi, nörolojik semptom ve bulgular

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Correspondence: Meltem Karacan Gölen, Department of Neurology Konya State Hospital, Konya, Turkey.
E-mail: drmeltemkaracan@hotmail.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in December 2019 and spread all over the world causing significant damage to our daily life. This epidemic was declared a pandemic by the World Health Organization on March 11th, 2020 (1-2). It was named SARS-CoV-2 because of its similarity to the SARS-CoV virus that previously caused a pandemic (3).

There is no consensus on how SARS-CoV-2 infects the central nervous system (CNS). Although the immunopathogenesis of SARS-CoV-2 is not fully known, we can benefit from information about the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, which previously caused pandemics. SARS-CoV-2 is a 10 nm-sized, spherical or oval RNA virus with viral membrane proteins on its surface (4). Several mechanisms for the spread of SARS-CoV-2 to the CNS have been proposed. The most common via is the respiratory system. SARS-CoV-2 attaches to the angiotensin-converting enzyme (ACE)-2 receptors on the cell surface via spike proteins. ACE-2 receptors are commonly found in the lungs, also in the mouth, nasal mucosa, skin, heart, arteries, kidneys, bone marrow, spleen, muscle tissue, adipose tissue, reproductive system, and brain. ACE-2 receptors are concentrated in the thalamus, cerebellum, the inferiorolivar nucleus surface of the brain, especially in the brainstem, where there are nuclei that control the cardiovascular and respiratory system. The absence of the blood-brain barrier allows neurotoxic molecules to damage these areas more easily (5-6).

There are ongoing studies on this subject, and among the spreading mechanisms of SARS-CoV-2, hematogenous spread and retrograde axonal spread are the most accepted mechanisms. Among the neuronal system damage mechanisms, hypoxic damage, cerebrovascular damage, and immune system-mediated damage mechanisms are often suggested (7). It has been reported that in hematogenous spread, SARS-CoV-2 can pass into the systemic circulation by passing through the cribriform plateau of the ethmoid bone, and even via retrograde central invasion with the microcapillary network in this area (8).

Hypoxia that develops in patients with severe pneumonia causes brain damage and brain edema. Toxic components due to peripheral vasodilation, hypercarbia, hypoxia, and anaerobic mechanisms accelerate this process (9). Immune-mediated damage also leads to cytokine storm by increasing inflammatory cytokines, activated T-lymphocytes, macrophages, and endothelial cells. Thus, with the increase of interleukin (IL)-6 levels, vascular leakage, complement cascade activation, and widespread intravascular coagulation with activation of the coagulation cascade cause end-organ damage (10).

As a result of research, it was thought that autoimmunity, adaptive immunity, and immune deficiency were effective in the neurotropism of SARS-CoV-2. Astrocytes and microglia defend against trauma and damage in the brain. Especially in viral infections, astrogliosis occurs primarily by being affected by astrocytes, and as a result of the impairment of microglia, neurodegeneration, synaptic involvement, and demyelination occur due to blood-brain barrier disruption. As a result of the cellular damage caused by SARS-CoV-2 in the brain, neurodevelopmental, neurologic, and psychiatric disorders may occur (6).

Clinical findings of patients with COVID-19 range from asymptomatic disease to multiorgan failure and septic shock due to various pathways. Patients with COVID-19 frequently have clinical findings that affect the respiratory system such as fever, dry cough, sore throat, and dyspnea. In some patients, neurologic symptoms are observed in addition to these clinical findings, and in some cases, neurologic symptoms may be the only symptoms. Within the neurologic findings that may occur due to the spread of the virus to the CNS through various mechanisms, headache, dizziness, seizure, encephalitis, stroke, neuromuscular disorders and peripheral nervous system involvement can be seen (2-11).

In this study, we aimed to determine the accompanying neurologic findings in patients with polymerase chain reaction (PCR)-positive COVID-19 and moderate or severe pneumonia findings.

METHODS

In this study, the neurologic findings and examination characteristics of patients with confirmed COVID-19 diagnoses who were followed in the neurology department between April-October 2020 were retrospectively evaluated. Data were obtained by examining the files and electronic medical records of the patients followed by neurologists assigned to the pandemic ward.

The classification of the severity of COVID-19 infection in patients is based on the report from Wu and McGoogan (2020). Patients without pneumonia or with mild pneumonia were classified as having mild disease, patients with severe dyspnea and hypoxia requiring oxygen support were considered as having severe disease, and patients with respiratory failure requiring ventilation support, septic shock or multiple organ dysfunction were determined as critically ill (12). Patients with moderate-severe pneumonia who were followed in our inpatient ward and did not require intensive care follow-up were included in the study.

The study included patients over the age of 18 years with positive PCR tests on nasopharyngeal swabs and pneumonia detected in thoracic computed tomography. Neurologic symptoms were investigated in detail in the file scan. Patients with a history of malignancy, major psychiatric findings, patients with a history of rheumatologic disease, and patients who were transferred to the intensive care unit were not included in the study. Of the 213 patients whose files were scanned, 179 were included in the study. Neurologic symptoms such as new-onset headache, taste and smell disorder, cerebrovascular ischemic or hemorrhagic disease causing focal lateralized deficit after the diagnosis of COVID-19, dizziness, loss of consciousness, epilepsy, myalgia, psychomotor agitation, which the patients described during their hospitalization or follow-up, were added to the records.

The pain characteristics, localization and severity of patients who described headache during hospitalization were questioned and recorded. These findings were retrieved from the patients' files and archives. The headache was classified as 'mild' if it did not affect daily activities without other symptoms of COVID-19, 'moderate' if it partially interfered with daily activity, and 'severe' if it was too intense to allow daily activities

The laboratory values of the patients at the time of admission to the emergency department were examined. The normal ranges of these parameters are D-dimer (0-0.5) µg/mL, lymphocyte (1.26-3.35) $\times 10^3$/mL, thrombocytes (173-390) $\times 10^3$/µL, creatine kinase (CK) (10-145) IU/L lactate dehydrogenase (LDH) (25-248) U/L, ferritin (11-306.8) µg/L, and C-reactive protein (CRP) (0-8) mg/L. High and low values were determined according to these normal ranges.

In this study, we evaluated the neurologic findings of 179 patients with moderate-severe pneumonia, who were classified as having mild and severe disease according to the classification.

Approval was obtained from the Local Ethics Committee (Protocol No: 2020-2896) and the Ministry of Health for this study.

Statistical Analysis

The normality of the distribution of continuous variables was tested using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare non-normal numerical data between two groups. The Chi-square test was used to investigate the relationship between categorical variables. Median [25%-75%] and frequencies (%) were given as descriptive statistics. Statistical analysis was performed with SPSS for Windows version 24.0 and a p-value < 0.05 was accepted as statistically significant.

RESULTS

This study included 179 patients with moderate to severe pneumonia with a confirmed diagnosis of COVID-19. All patients had a positive

nasopharyngeal PCR swab test, and laboratory and imaging tests were compatible with COVID-19. Fifty-two percent (93/1790) of the patients were male and 48% (86/179) were female. Considering the symptoms at admission to the hospital, fatigue myalgia was seen in 80/179 (44.6%) patients, dyspnea in 72/179 (40.2%), cough in 65/179 (36.3%), fever in 52/79 (29%), and 35/179 (19.5%) patients had diarrhea. The mean age of the patients was 60.34 ± 15.25 years. More than half (60.3%) of the patients had an additional chronic disease. The most common chronic disease was hypertension in 59/179 (33%), diabetes mellitus in 56/179 (31.3%), coronary artery disease in 13/179 (7.3%), chronic obstructive pulmonary disease in 13/179 (7.3%), asthma in 18/179 (10.1%), and 36/179 (20.1%) patients had other diseases (e.g. chronic kidney failure, oncologic disease). Findings consistent with unilateral COVID pneumonia were observed in 45/179 (25.1%) of the patients, and 134/179 (74.9%) had lung involvement. About one-fifth, 35/179 (19.6%), of the patients were current smokers. The mean hospitalization period of the patients was 7.1 ± 3.52 days (Table 1).

Table 1: Demographic and Characteristics of Patients with COVID- 19

Characteristics		Results (n=179)	
		Mean±SD	Median (min-max)
Age (y)		60.34 ± 15.25	61 (19-91)
		n	%
Gender	Male	93	52
	Female	86	48
CoreSymptoms	Cough	65	36.3
	Fever	52	29
	Dyspnea	72	40.2
	Fatigue	80	44.6
	Diarrhea	35	19.5
AdditionalDisease	Diabetes mellitus	56	31.3
	Hypertension	59	33
	Cardiovascular diseases	13	7.3
	COPD	13	7.3
	Asthma	18	10.1
	Other diseases	36	20.1
	Smoking	35	19.6
Lunginvolvement		179	100
Unilateral		45	24.1
Bilateral		134	74.9
Length of stay (days), mean±SD (min-max)		7.1±3.52	3-29

The rate of headache at admission or during hospitalization was 101/179 (56.4%). Mild pain was reported in 26/101 (25.7%) patients, moderate pain in 50/101 (49.5%), and severe pain in 25/101 (24.7%) patients. The pain was all over the head in 48/101 (48.5%) patients and localized to the bilateral temporal regions in 53/101 (52.5%) patients. The pain was felt as compression in 61/101 (60.4%) patients and throbbing pain in 40/101 (39.6%).

Dizziness was observed in 33/179 (18.4%) patients, and changes in consciousness were observed in 20/179 (11.2%) patients. Among the cerebrovascular diseases, acute ischemic cerebrovascular disease was observed in five (2.8%) patients and hemorrhagic cerebrovascular disease was observed in one (0.6%) patient. In the etiologic examination of the group with ischemic cerebrovascular disease, it was found that two patients had cardioembolic events and three had ischemia due to a large artery occlusion.

Loss of smell was detected in 62/179 (34.6%) patients and taste disturbance was detected in 52/179 (29%) patients. Epileptic seizure was observed in 1/179 (0.6%) patient. Psychomotor agitation was observed in 18/179 (10%) patients (Table 2).

Table 2: Neurologic Symptoms of Patients with COVID-19

Neurologic symptoms		n	%
Headache		101	56.4
Dizziness		33	18.4
Altered consciousness		20	11.2
Myalgia		80	44.6
Loss of smell		62	34.6
Taste disturbance		52	29
Acute Cerebrovascular Diseases	Ischemic	5	2.8
	Hemorrhagic	1	0.6
Seizure		1	0.6
Psychomotor agitation		18	10

Myalgia symptoms were detected in 80 (44.6%) of 179 patients. The mean CK values were 182.0 ± 137.02 U/L (min 129.00 U/L, max 721 U/L) (median [25%-75%] 167 [145-198] in patients with myalgia, whereas they were 71.67 ± 83.80 U/L in patients without myalgia (min 21 U/L, max 352 U/L) (median [25%-75%] 87 [52-101]. We found a significant relationship between myalgia and increased CK levels (p = 0.001)

Laboratory findings of patients with neurologic symptoms accompanying COVID-19 findings were compared with patient groups without neurologic findings. There was no statistically significant difference in laboratory parameters (lymphocytes, platelets, D-dimer, troponin, ferritin, CRP, and CK) between the groups with and without headache, and with and without smell-taste disorders (Table 3).

When the laboratory parameters of the patients were evaluated, lymphopenia (1.31 ± 0.63 x10^3/m) was observed in 92/179 (51%). When the platelet counts were examined, thrombocytopenia (239.41 ± 90.65 x10^3/μL) was seen in 45/179 (2.4%) patients, and thrombocytosis was present in 10/179 (5.6%) patients; 124/179 (69%) patients were found to be normal. Among the acute-phase reactants, an increase in CRP (77.56 ± 92.96 mg/L) was observed in 160/179 (89%) patients, and increased ferritin (271.3 ± 264.34 μg/L) was observed in 48/179 (27%). An increase in D-dimer (1.11 ± 3.42 μg/mL) was observed in 34% (60/179) of our patients. Seventeen percent (30/179) of the patients had an increase in CK 75 (56-118 IU/L) and 20% (35/179) had an increase in LDH (280.23 ± 14.22 IU/L). Troponin was found to be high in 39/179 (21.8%) patients. A prolonged prothrombin time was detected in 52/179 (29%) patients (Table 4).

Table 3: Relationship of Neurologic Findings with Laboratory Parameters

	Headache			Myalgia			Loss of smell and taste disturbance		
	With (n=101)	Without (n=78)		With (n=80)	Without (n=99)		With (n=86)	Without (n=93)	
Laboratory Findings	Median [25%-75%]	Median [25%-75%]	P	Median [25%-75%]	Median [25%-75%]	P	Median [25%-75%]	Median [25%-75%]	P
Lymphocyte ×10^3/uL	1.29 [0.92 -1.6]	1.18 [0.94 -1.64]	0.652	1.21 [0.94 -1.64]	1.29 [0.93 -1.63]	0.999	1.23 [0.92 -1.59]	1.21 [0.95 -1.65]	0.896
Platelet ×10^3/uL	216 [187 -270]	227 [170 -292]	0.964	218 [182 -289]	220 [175 -281]	0.586	224.5 [190 -299]	209 [174 -284]	0.197
D-Dimer ng/mL	0.36 [0.22 -0.67]	0.4 [0.22 -0.89]	0.250	0.34 [0.2 -0.72]	0.41 [0.24 -0.89]	0.163	0.33 [0.62 -0.19]	0.41 [0.82 -0.31]	0.062
Troponin ng/L	6.8 [1.3-255]	5.3 [0.4 - 175]	0.617	5.65 [3.2 -11]	6.6 [3.3 -10]	0.884	6.95 [3.7 -12.1]	6 [3.2 -10.3]	0.791
Ferritin ng/mL	178 [84.5 -316]	182 [113 -397.2]	0.254	160 [89.2 -309]	194.5 [116 -450]	0.078	174.2 [85 -358]	182 [101 -350]	0.700
C reactive prorein (CRP) mg/L	52 [19 -86.9]	64.9 [22 -115]	0.231	52 [19 -95.3]	56 [23 -110]	0.438	44.95 [13 -83.9]	64.8 [23.7 -114]	0.065
Creatin Kinase (CK) IU/L	132 [90 -178]	134.5 [78 -176]	0.438	167 [145 -198]	87 [52 -101]	0.001*	65 [45 -120]	135 [90 -178]	0.069

*Significant at 0.05 level, Mann-Whitney U test

Table 4. Laboratory Findings of Patients with COVID-19

Laboratory findings (Normal range)	Finding levels*					
	Normal		High		Low	
	n	%	n	%	n	%
Lymphocyte (1.26-3.35) $\times 10^3$/mL	50	28.4	37	20.6	92	51
Platelet (173-390) $\times 10^3/\mu L$	124	69	10	5.6	45	25.4
C Reactive Protein (CRP) (0-8) mg/L	19	11	160	89		
Ferritin (11-306.8) µg/L	131	73	48	27		
D-dimer (0-0.5) µg/mL	119	66	60	34		
Creatinekinase (CK) (10-145) IU/L	149	83	30	17		
Troponin (0-19.8) ng/mL	140	78.2	39	21.8		
Lactate Dehydrogenase (LDH) (25-248) U/L	144	80	35	20		
Prothrombin time (PT) (8.40-10.6) sec	127	71	52	29		

*Data presented asfrequency (n) and percentages (%).

Considering the relationship between sex and neurologic diseases, no statistically significant difference was observed between the sexes and symptoms of headache, smell-taste disorder, and myalgia (Table 5).

Table 5: Relationship between Sex and Neurologic Disease

		SEX				
		Male		Female		
		n	%	n	%	p
Acute Cerebrovascular Disease	Yes	3	3.2	3	3.5	0.922
	No	90	96.8	83	96.5	
Headache	Yes	49	52.7	52	60.5	0.294
	No	44	47.3	34	39.5	
Myalgia	Yes	40	42,9	40	46.4	0.637
	No	53	56,9	46	53.5	
Loss of smell and taste disturbance	Yes	48	51,7	38	44.2	0.987
	No	45	48,3	48	55.8	

*Significant at 0.05 level, Chi-square test.

DISCUSSION

COVID-19 can lead to life-threatening symptoms due to its specific immunologic properties. A new perspective in the field of neurology has come to the fore because COVID-19 causes neurologic symptoms in addition to respiratory system symptoms.

Among the neurologic symptoms that may occur due to the spread of the virus to the CNS through various mechanisms are headache, dizziness, seizures, encephalitis, stroke, and neuromuscular disorders, and peripheral nervous system (PNS) involvement can also be listed.

In this study, we evaluated the accompanying neurologic symptoms of 179 patients with moderate-to-severe pneumonia with positive COVID-19 PCR tests during their diseases. Many studies have been conducted to evaluate the neurologic symptoms accompanying COVID-19. In a study of 214 patients by Mao et al., neurologic findings were classified as CNS, PNS, and musculoskeletal system findings. In this study, nervous system findings were observed in 36.4% of the patients. Among the CNS findings, which were present in 24% of the patients, the most common symptom was dizziness (16.8%), followed by headache (13.1%). Smell and taste disturbances were observed among the PNS findings. In a study conducted in Washington, CNS involvement was observed in 208 (51.5%) of 404 patients with COVID-19 (13-14).

In our study, headache was the most common neurologic symptom with a frequency of 56.4%. In the retrospective study of Wan et al., the frequency of headache was reported as 33% (15).

In a metanalysis by Borges et al., headache was detected in 12% of 3598 patients, and Moro et al. found the frequency of headache as 61.9%. (16,17). Headache in COVID-19 is one of the most common accompanying neurologic symptoms and can sometimes be observed as the only symptom. Several mechanisms are responsible forthe headache. Direct involvement of peripheral trigeminal nerve endings, inflammation of endothelial cells, hypoxia and dehydration are thought to be possible mechanisms that can cause headache. Activation of the trigeminovascular pathway is the most common mechanism among headache formation mechanisms. In addition, abnormal regulation (vasoconstriction, oxidative stress and free radical formation) caused by excessive ACE2 expression of ACE receptors and inflammation in endothelial cells may play a role in trigeminovascular activation and cause headache (18).

In our study, it was found that the headache characteristics included sudden onset, moderate level of pain nonresponding to analgesics, involvement of temporal regions and increased severity with bending forward. For the most part, the pain was constricting. It was observed that only a small number of patients had pain similar to the characteristics of migraine and tension-type headache. According to the observations of Bolay et al., the features of the ongoing headache in COVID-19 may be new-onset, moderate-severe, bilateral temporal spread, constrictive or throbbing (18) .

In our study, dizziness was observed in 33/179 (18.4%) of patients. In the study by Karadaş et al. performed on 239 patients, the frequency of headache was reported as 27.6%, and dizziness was reported as 16%. This situation suggested that all patients included in the study had moderate-to-severe pneumonia and moderate hypoxia secondary to pneumonia caused dizziness symptoms. No pathology was observed in the cranial system imaging (19).

A change in consciousness was observed in 11.2% of the patients included in the study at the time of admission or hospitalization. Change in consciousness due to infectious diseases is a common clinical situation, especially in the elderly. It has been reported that 14.8% of patients diagnosed as having COVID-19 have altered consciousness during the disease processes (13). The majority of the patients with COVID-19 who presented with encephalopathy were aged over 50 years, and the cranial imaging and cerebrospinal fluid (CSF) analysis of these patients were within normal limits.

Smell and taste disturbances are common symptoms in patients with COVID-19. Olfactory and taste disturbances are the most common findings of the PNS in patients with COVID-19. The olfactory nerve endings in the nasal area are blamed for the smell and taste disturbances. In a retrospective Chinese study of Mao et al., smell and taste disturbances were present in 5.7% and 5.1% of the patients, respectively (13). In the study of Menni et al., including 1702 patients, smell and taste disturbances were observed in 59.4% of the patients (20). In a prospective European study of 417 patients, 85.6% were found to have olfactory and 88% had gestatory dysfunction (21). In our study, smell and taste disturbances were observed in 34.6% and 29% of the patients, respectively.

It has been proven that the development of cerebrovascular disease in patients with COVID-19 is too common to ignore. It was thought that there was an increase in cerebrovascular events due to the increase in the acid concentration in the circulation due to hypoxia leading to cerebral edema and decreased cerebral blood flow. In addition, it has been shown that the risk of cerebrovascular disease increases by activating the cytokine cascade as a result of hypoxia. Additional comorbid conditions such as advanced age, coronary artery disease, diabetes mellitus, and hypertension accelerate this process (22). In our study, acute cerebrovascular ischemic disease was observed in 2.8% of the patients at their first admission or hospitalization. Three of the patients with ischemic cerebrovascular disease died during the hospitalization period. Acute cerebrovascular hemorrhagic disease was observed in 0.6% of the patients. Some patients who presented with cerebrovascular disease were followed in intensive care due to their clinical

conditions, thus this group of patients was smaller in our case series. Cerebrovascular disease was observed in 3.8% of patients with COVID-19 in a study by Karadaş et al (19). In the retrospective study of Lodigiani et al. in which 338 patients were evaluated, cerebrovascular disease was observed in 2.5% of the patients (23).

Myalgia and arthralgia symptoms are quite common in patients with COVID-19, which significantly affect the daily life of the patients. The SARS-Cov-2 virus is thought to affect the ACE-2 receptors that have settled in the muscles. In addition, it is thought that proinflammatory cytokines, which increase during disease, are responsible for muscle and joint involvement (24). In another study investigating the relationship between myalgia and CK levels in patients with COVID-19, 140 of 239 patients had high CK levels and 32 patients with high CK had myalgia. The mean CK values in patients with myalgia and without myalgia were 241.05 ± 137.02 U/L (min 45.00 U/L, max 721 U/L), and 139.67 ± 83.80 U/L (min 21 U/L, max 451 U/L), respectively. CK levels were found to be high in 30% of our patients. Similar to our study, the study also found a significant relationship between myalgia and increased CK levels (p=0.001) (19). In the study conducted by Mao et al., myalgia and arthralgia were detected in 23% of patients. It was also reported that increased CK level and muscle pain were observed 10.7% of patients with severe COVID-19 (13). In our study, a significant increase in CK levels was observed in the group with myalgia (80/179) when compared with the group without myalgia (p=0.001). There was no statistically significant difference in laboratory parameters in the group with headache and smell-taste disorder compared with the group without.

Epileptic seizure was observed in one patient (0.6%). Although significant seizure activity was observed in electroencephalography (EEG), cranial imaging tests were found to be normal. Seizure control was achieved by treating the patient according to the status epilepticus protocol. When all the studies are reviewed, the issue of seizure development secondary to infection due to COVID-19 has not yet been clarified, and it can be predicted that neuronal damage due to virus-related CNS complications may lead to secondary epileptic seizures (25). In patients diagnosed with COVID-19, lymphopenia and marked changes in thrombocyte levels have been observed. Lymphopenia was observed in 51% of patients, and thrombocytopenia was observed in 25.4%. Guan et al. reported that lymphopenia developed in 83.2% of patients and thrombocytopenia developed in 36.2% (26). It was found that lymphopenia was associated with the development of ARDS and the risk of patients needing intensive care (26,27).

In our study, CRP values were found to be significantly higher (77.56 ± 92.96 mg/L) (min-max 0-8 mg/L) in 160 of the patients (89%). It is known that the increase in CRP provides better information compared with decreased lymphocyte ratios in evaluating the degree of disease progression in the early stage of COVID-19. Ferritin values were found high in 49% of our patients. An increase in LDH was detected in 20% of our patients. It was reported that the need for intensive care and mortality rates are increased in patients with high LDH levels (28).

Increased D-dimer (1.11 ± 3.42 [min - max 0-0.5] µg/mL) was observed in 34% of the patients. High D-dimer levels and severe lymphopenia were found to be directly proportional to the high mortality rates (29,30).

Limitations of the Study

Our study had some limitations. This study was conducted in a single center. The patients included in the study were eligible for follow-up in a pandemic clinic. Patients with severe pneumonia findings and severe clinical findings with neurologic symptoms were not included in the study because they were followed up in the intensive care unit. We obtained the data through the patient files retrospectively. Therefore, we could only use the test results recorded in the files. Cranial imaging was performed in a limited patient group due to the pandemic. Moreover, CSF analysis, advanced blood tests, and electrophysiologic examinations of these patients could not be performed.

Therefore, detailed evaluations are needed in more comprehensive case series.

Neurologic findings can be observed at the beginning, during the course of COVID-19 infection, or chronic period of the COVID-19 disease. Currently, there is insufficient information about the long-term effects of COVID-19. Therefore, multi-center detailed studies with larger case series are needed to diagnose, prevent, and treat neurologic effects in the acute and chronic stages.

Conclusion

COVID-19 is an important disease that affects the CNS as well as the respiratory system and can cause various symptoms. It should be kept in mind that neurologic findings can be seen throughout the disease course and chronically. Neurologic symptoms, which may negatively affect the clinical course and increase mortality and morbidity, should be carefully evaluated. It should also be kept in mind that a single neurologic finding can be the only symptom of COVID-19. More detailed clinical, laboratory, biomarker, and neuropathologic studies will help to elucidate the underlying pathobiologic mechanisms.

Conflict of Interest
There is no conflict of interest.

Financial Support
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Ethics Committee Approval
Ethical approval was obtained the Local Ethics Committee (Protocol No: 2020-2896) and the Ministry of Health for this study.

Informed Consent
This a retrospective study.

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