

COVID-19 Hastalarında İnme Sıklığının Değerlendirilmesi

Evaluation of Stroke Frequency in COVID-19 Patients

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ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVID-19) hastalarında merkezi ve periferik sinir sisteminin farklı mekanizmalarla tutulumuna bağlı olarak nörolojik semptomlar ortaya çıkmaktadır. COVID-19 enfeksiyonunda sitokin artışı ile birlikte protrombotik aktivasyon ile mikrovasküler tromboz gelişmektedir. Bu çalışmada COVID-19 pozitif hastalarda serebrovasküler hastalık insidansını ve eşlik eden risk faktörlerini araştırmayı amaçladık.

Materyal ve Metot: COVID-19 tanısı alan hastalarda hastalıkla ilişkili olarak ortaya çıkan serebrovasküler hastalık durumu değerlendirildi. Serebrovasküler olaylar iskemik ve hemorajik olaylar, geçici iskemik ataklar ve serebral ven trombozu olmak üzere 4 grupta değerlendirildi. Bu hastalarda serebrovasküler hastalık için risk faktörleri ve bu risk faktörlerinin COVID-19 hastalarında serebrovasküler hastalık durumunda prognoza etkisi değerlendirildi.

Bulgular: Çalışmada COVID-19 tanısı alan 1000 hasta değerlendirildi. On dört hastada (%1,4) iskemik serebrovasküler hastalık ve/veya geçici iskemik atak geliştiği görüldü. Bu durum COVID-19 tanısı alındıktan sonraki ilk hafta içinde izlendi. COVID-19 ile teşhis edilen akut iskemik inme 14 hastada COVID-19 ile ilgili en yaygın semptomlar ateş ve solunum sıkıntısı idi.

Sonuç: COVID-19, birden fazla risk faktörü olan hastalarda inme riskini artırıyor. Özellikle pulmoner tutulumlu ve akut iskemik inmeli hastalarda mortalite daha yüksek olabileceğinden yakın takip daha dikkatli yapılmalıdır.

Anahtar Kelimeler: COVID-19, inme, serebrovasküler hastalık

ABSTRACT

Objective: Neurological symptoms occur due to central and peripheral nervous system involvement with different mechanisms in coronavirus disease 2019 (COVID-19). Microvascular thrombosis develops with prothrombotic activation along with the increase in cytokines in COVID-19 infection. We aimed to investigate the incidence of cerebrovascular disease and concomitant risk factors in COVID-19 positive patients.

Materials and Methods: Acute and temporally related cerebrovascular diseases with a diagnosis of COVID-19 were evaluated. Cerebrovascular events were assessed in 4 groups as ischemic and hemorrhagic events, transient ischemic attacks, and cerebral venous thrombosis. Risk factors for cerebrovascular disease in these patients were also assessed, and which risk factors for cerebrovascular diseases in COVID-19 patients are high risk were examined.

Results: Of the 1000 patients with COVID-19 disease were evaluated. Ischemic cerebrovascular disease and/or transient ischemic attack were found in 14 patients (1.4%). The most common symptoms related to COVID-19 were fever and respiratory distress in 14 patients with acute ischemic stroke diagnosed with COVID-19.

Conclusion: COVID-19 increases the risk of stroke in patients with multiple risk factors. Close follow-up should be performed more carefully, especially in patients with pulmonary involvement and acute ischemic stroke, because mortality is likely to be higher.

Keywords: Cerebrovascular disease, COVID-19, stroke

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Yayın Bilgisi / Article Info:

Gönderi Tarihi/ Received: 08/02/2022

Kabul Tarihi/ Accepted: 06/07/2022

Online Yayın Tarihi/ Published: 10/12/2022

INTRODUCTION

Acute ischemic stroke (AIS) is a life-threatening complication of coronavirus disease 2019 (COVID-19) infection. While much is still unknown about the novel coronavirus, the link between COVID-19 and ischemic stroke has been increasingly documented in the literature. It has been observed that neurological symptoms and signs are noted in approximately 30% of patients with COVID-19.^{1,2} Neurological symptoms occur due to central and peripheral nervous system involvement with different mechanisms in COVID-19 patients. The most common neurological symptom is a headache. Alterations in consciousness, taste disorders, hyposmia, acute cerebrovascular disease, encephalitis, myelitis, epilepsy, and Guillan-Barre syndrome have also been observed. The neurological picture is more severe in patients with comorbidities such as hypertension, and the inflammatory response is more pronounced.³ Widespread microvascular thrombosis has been reported which occurs with prothrombotic activation along with the increase in cytokines in COVID-19 infection, and high D-dimer levels are seen in these patients. The new American Heart Association and American Stroke Association guideline emphasizes that stroke occurs in 5.9% of COVID-19 patients on average ten days after symptom onset.⁴ Furthermore, the first observations are that cerebrovascular disease is frequently found in the group with a poor prognosis of COVID-19 patients.⁵ Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a prothrombotic state causing venous and arterial thromboembolism and elevated D-dimer levels.² Endothelial and mononuclear cell activation may trigger the coagulation process and increase thrombin generation in severe COVID-19 infection. Free thrombin circulation not controlled by natural anticoagulants can activate platelets and cause thrombosis. Although ischemic stroke is recognized as a complication of COVID-19 (usually in severe disease), the mechanism is not yet understood. As a result, early anticoagulant treatment with low-molecular-weight heparin will reduce the risk of ischemic stroke in COVID-19 patients.^{6,7} The onset of ischemic cerebrovascular disease in COVID-19 patients varies widely in the literature. While some patients develop ischemic stroke 1-2 weeks after diagnosis with typical COVID-19 symptoms, others develop symptoms such as fever, dry cough, and shortness of breath during ischemic stroke follow-up and are subsequently diagnosed with COVID-19. The most striking common feature of these patients is high D-dimer levels ($\geq 1000 \mu\text{g/L}$).⁸ COVID-19 patients may experience neurologic symptoms first, such as acute cerebrovascular dis-

ease. Therefore, SARS-CoV-2 infection should be kept in mind in patients presenting with the aforementioned neurologic symptoms during the pandemic to prevent delay in diagnosis and spread.⁷

This study aims to investigate the incidence of cerebrovascular disease and concomitant risk factors in COVID-19 positive patients.

MATERIALS AND METHODS

Ethics Committee Approval: Patients hospitalized in Erciyes University Faculty of Medicine Hospital between July 2020 and December 2020 with a diagnosis of COVID-19 in the Pandemic Unit were included in our study retrospectively. The study was carried out under the Helsinki declaration and was approved by Erciyes University ethics committee (Date: 06/01/2021, decision no: 2021/14). In this time period 1000 patients data were evaluated. In all patients, the diagnosis of COVID-19 disease was made by evaluating reverse transcription-polymerase chain reaction test (PCR) and lung tomographies. Patients who had a diagnosis of cerebrovascular disease or transient ischemic attack in two weeks and COVID-19 PCR test results were positive in this time period included in the study. Patients with positive COVID-19 PCR test results but don't have cerebrovascular event and patients with negative COVID-19 PCR test results were excluded. Diagnosis of stroke was made by neurologist. Patient contact information and COVID-19 PCR test result were obtained from the public health management system (hsys.saglik.gov.tr). Patients demographics, history of acute cerebrovascular disease, brain computed tomography and/or magnetic resonance images, additional medical conditions, medications, blood cholesterol levels, routine blood biochemical tests, laboratory data such as hemogram, C-reactive protein (CRP), D-dimer were scanned from electronic medical records. Acute and temporally related cerebrovascular diseases with a diagnosis of COVID-19 were evaluated. Cerebrovascular events were assessed in 4 groups as ischemic and hemorrhagic events, transient ischemic attacks, and cerebral venous thrombosis. Etiology of ischemic stroke was determined according to trial of ORG 10172 in acute stroke treatment (TOAST) classification. The risk factors for cerebrovascular disease in these patients were also assessed, and which risk factors placed COVID-19 patients at higher risk for cerebrovascular diseases were examined. The relationship between COVID-19 and cerebrovascular disease has been studied. National Institutes of Health Stroke Scale (NIHSS) scores were recorded at admission and discharge, as were Modified Rankin Scale (mRS) scores at discharge. The NIHSS is a standardized test to determine stroke severity in the emer-

gency department. The modified Rankin score is the test used to detect dependence and assess functional survival.

Statistical Analysis: Continuous variables were presented with descriptive statistics, mean, standard deviation, minimum and maximum values, and categorical variables were presented numbers and percentages. To determine whether the numerical data of the variables conform to the normal distribution, a one-sample Kolmogorov-Smirnov test was performed. The chi-square test was used to determine the relationship between groups and categorical variables. If the numerical data were normally distributed, the Student's t-test was used to compare paired groups, and the Mann-Whitney U test was used for paired groups that did not fit normally. These analyses were carried out using the SPSS version 21.0 (IBM Corp., Armaonk, NY, USA). $p < 0.05$ was considered statistically significant.

RESULTS

A thousand patients with COVID-19 disease were evaluated. Ischemic cerebrovascular disease and/or transient ischemic attack were found in 14 patients (1.4%) (11 ischemic events, 3 transient ischemic attacks). There was no hemorrhagic stroke and cerebral venous thrombosis. The mean age of patients diagnosed with acute cerebrovascular event was 67 (50-82). Eight of the patients were male, and 6 were female. The most common symptoms related to COVID-19 were fever and respiratory distress in 14 patients with acute ischemic stroke diagnosed with COVID-19. Other symptoms included weakness, muscle pain, and cough. The mean admission glucose values of the patients were 151 (89-374)mg/dl, lymphocyte values were $1.2 \times 10^3 (0.07-2.40) \mu\text{L}$, D-dimer values in one patient were 14540 $\mu\text{gr/L}$, whereas the mean value was 2445 (430-14540) $\mu\text{gr/L}$. The mean CRP value was 90(4-213) mg/L. At the time of admission, the mean leukocyte value was $6200(2650-42130) \times 10^3/\mu\text{L}$ (Table 1).

Table 1. Laboratory results in COVID-19 patients.

Parameters	All Patients(n:14) Mean \pm SD/median (min-max)
Leukocytes ($\times 10^3/\mu\text{L}$)	6200(2650-42130)
Lymphocyte ($\times 10^3/\mu\text{L}$)	1.2(0.07-2.40)
Hemoglobin (g/dl)	11.8 \pm 2.11
Platelet ($\times 10^3/\mu\text{L}$)	249.6 \pm 118
MPV	10.5 \pm 1.4
Troponin (mg/dl)	0.049 (0.01-0.42)
D-Dimer ($\mu\text{gr/L}$)	890 (430-14540)
CRP (mg/L)	81.15 (4.3-213)
Glucose (mg/dl)	122(89-374)
BUN (mg/dl)	21.4(14.4-70.7)
Creatinine (mg/dl)	1.33(0.84-4.63)
AST (u/L)	40(18-166)
ALT (u/L)	19.7(9.95-66.3)
CPK (u/L)	55.7 (25-725)
TC (mg/dl)	126 (58.6-192)
LDL (mg/dl)	71.3 (26.4-128)
Tg (mg/dl)	105 (69.5-199)
HDL (mg/dl)	31.4 \pm 11.6

SD: Standard deviation; MPV: Mean platelet volume; CRP: C Reaktif protein; BUN: Blood urea nitrogen; AST: Aspartat aminotransferase; ALT: Alanin aminotransferase; CPK: Creatine phosphokinase; TC: Total cholesterol; LDL: Low density lipoprotein; Tg: Trilycerides; HDL: High density lipoprotein.

Brain tomography and diffusion magnetic resonance imaging were studied in all patients. Regarding infarct localization, four patients had posterior system infarction (1 right posterior cerebral artery distal branches, 1 posterior inferior cerebellar artery, 1 patient basilar perforating arteries), eight patients had anterior system infarction(7 patients middle cerebral artery M2, M3 and M4 distal branches, 1 patient Anterior cerebral artery distal branch), and two patients had multiple infarct areas. There were no large vessel occlusions.NIHSS score on admission was 11 in 1 patient, the mean admission NIHSS score was 2.2(0-11). The mean discharge NIHSS

score was 1.1(0-4). Four patients with stroke and pulmonary involvement died. Those who were discharged had a mean modified Rankin score (mRS) of 2. In the evaluation of comorbidities, hypertension (HT) was found in 4 patients (28.6%), diabetes mellitus (DM) in 3 patients (21.4%), HT and DM in 3 patients (21.4%), HT and previous ischemic cerebrovascular disease (ICVD) in 2 patients (14.3%), heart failure (HF) in 2 patients (14.3%) and atrial fibrillation (AF) in 4 patients (28.6%). At least one of the risk factors such as HT, DM, and AF was present in 92.9% of patients (Table 2).

Table 2. Age and chronic disease, medication used.

All Patients(n:14)		
Age	Mean±SD	67.9±8.5
Risk Factors n (%)	At least one risk factor (+)	13 (92.9)
	HT	9 (64.3)
	DM	6 (42.9)
	Past stroke	2 (14.3)
	AF	4 (28.6)
	No	1 (7.1)
	HT+past stroke	2 (14.3)
	AF+HT+DM	2 (14.3)
	AF+DM	1 (7.1)
	HT+CVD	2 (14.3)
	HT+AF	1 (7.1)
Medication n (%)	ASA+LMWH	5 (35.7)
	Clopidogrel+LMWH	3 (21.4)
	Heparin	1 (7.1)
	ASA+Clopidogrel	2 (14.3)
	Heparin+Clopidogrel	1 (7.1)
	ASA	1 (7.1)
	Coumadin	1 (7.1)
Gender (M)	n (%)	8 (57%)
Symptom n (%)	Fever	2 (14.3)
	Malaise	5 (35.7)
	Muscle Pains	1 (7.1)
	Cough	2 (14.3)
	Breathing Difficulty	4 (28.6)
CVD n (%)	Ischemic CVD	11 (78.6)
	TIA	3 (21.4)
Infarct Location n (%)	Frontal+Cerebellar	1 (7.1)
	Frontal	1 (7.1)
	Frontotemporal	1 (7.1)
	Multiple	2 (14.3)
	Occipital	2 (14.3)
	Cerebellum	2 (14.3)
	Splenium	1 (7.1)
	Watershed	1 (7.1)

SD: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, CVD: Cerebrovascular disease, TIA: Transient ischemic attack, ASA: Acetylsalicylic acid, LMWH: Low molecular weight heparin.

According TOAST classification 4 patients etiology was cardioembolism, 10 patients etiology was atherosclerosis (Table 3). Eleven patients admitted to emergency department with a stroke clinic, 3 pa-

tients had a stroke while they were hospitalized for COVID-19. All three patients had stroke in the first week of admission.

Table 3. Characteristics of Stroke patients with COVID-19.

Patient	Risk Factors	Baseline NIHSS	Infact Localization	Etiology	Treatment	Discharge NIHSS	Prognosis (3rd-month mRS)
1	HT	3	Splenium	Atherothrombosis	Medical	0	0
2	DM	6	Frontotemporal	Atherothrombosis	Medical	4	1
3	HT+CVD	8	Occipital	Atherothrombosis	Medical	5	6
4	HT+AF	8	Cerebellar	Cardioembolism	Medical	6	2
5	HT	0	No	Atherothrombosis	Medical	0	0
6	AF+HT+DM	7	Watershed	Cardioembolism	Medical	3	6
7	HT	5	Frontal	Atherothrombosis	Medical	5	6
8	HT+CVD	5	Parietal	Atherothrombosis	Medical	0	0
9	DM	8	Multiple	Atherothrombosis	Medical	8	6
10	AF+HT+DM	3	Multiple	Cardioembolism	Medical	0	0
11	AF+DM	11	Occipital	Cardioembolism	Medical	4	1
12	-	0	No	Atherothrombosis	Medical	0	0
13	DM	0	No	Atherothrombosis	Medical	0	0
14	HT	6	Pons	Atherothrombosis	Medical	4	2

HT: Hypertension; DM: Diabetes mellitus; AF: Atrial fibrillation; CVD: Cerebrovascular disease.

DISCUSSION AND CONCLUSION

In this study, the rate of stroke in the patient group with positive COVID-19 infection was determined as 1.4%. From the onset of the pandemic until now, the incidence of stroke in COVID-19 infection has varied. Studies have shown that the incidence of stroke in patients with COVID-19 infection ranges from 0.9% to 2.7%. Similar to our study, stroke was detected in 23 (1.4%) of 1683 patients admitted to Spain between March and April 2020 with a diagnosis of COVID-19. Of these, 17 had an ischemic stroke (73.9%), 2 had arterial dissection, 5 had an intracerebral hemorrhage, and 1 had leukoencephalopathy. This study found that stroke risk factors such as HT, DM, and AF were higher in COVID-19 patients who suffered an acute ischemic stroke, and the mortality rate was two times higher than in patients who had not suffered a stroke.⁹ In our study, 92.9% of patients had at least one of the risk factors, such as HT, DM, or AF for stroke.

In a study, Qureshi et al., evaluated 8163 patients diagnosed with COVID-19 and found that acute ischemic stroke developed in 103 (1.3%) patients.¹⁰ Ramos-Araque et al. found acute ischemic stroke in 156 (1.1%) of the 14,483 COVID-19 patients with a lab-confirmed diagnosis.¹¹ Cryptogenic stroke was the most commonly reported etiology, and it was found to be significantly correlated with high leukocytes, CRP, and D-dimer levels (55/129, 42.6%).

The coronavirus is not always limited to the respiratory tract and may first present with neurological symptoms. The neurological disorders associated with COVID-19 have been classified into five categories: encephalopathies, inflammatory syndromes, strokes, peripheral neuropathies, and other central nervous systems (CNS) disorders.¹² The possible pathophysiology of neurologic involvement is related to direct brain invasion by the virus or to virus-

related hyperinflammatory and hypercoagulable states and immune-mediated processes after infection. However, hypoxemia and endothelial dysfunction due to COVID-19 may also cause neurologic damage in the long term, so close monitoring of patients is essential to understand potential neurologic complications.¹³

Prothrombotic condition, hyperinflammatory response, cardiomyopathy and endothelial damage from direct viral invasion have been identified as potential mechanisms of SARS-CoV-2-associated stroke. Postmortem histologic examinations of patients infected with SARS-CoV-2 showed microvascular and macrovascular thrombosis with platelets, fibrin, red blood cells, and leukocytes in arterioles, capillary beds, and venules. This supports the fact that SARS-CoV-2 infects the respiratory tract and causes disease in the vascular bed.¹⁴

COVID-19 has been identified as an independent predictor of acute ischemic stroke in hospitalized patients and has been correlated with early mortality and poor survival in small observational studies.¹⁴ In the initial studies from Wuhan, infected patients with a history of stroke were found to have a high in-hospital mortality rate.¹⁵ In another study, Yaghi et al.,¹⁶ examined the rate of stroke in COVID-19 infected patients in New York at the beginning of the pandemic and showed that 0.9% of all patients hospitalized with COVID-19 were found to have an ischemic stroke, and 63.6% of these patients died. In our study, the mortality rate in COVID-19 patients with acute ischemic stroke was 29% (4/14). Although there is no patient with large vessel occlusion, the mortality was high in our cohort as in the literature.

In our study, all patients were found to have high leukocyte, D-dimer, and CRP levels. SARS-CoV-2 infection is known to be associated with a prothrom-

botic state with elevated D-dimer levels. D-dimer is a cross-linked fibrin degradation product that reflects blood clot formation and subsequent fibrinolysis. D-dimer has a very high sensitivity for the thrombotic state but low specificity. Several studies in patients with COVID-19 have shown a very strong association between continuously increasing D-dimer levels and severe disease/poor prognosis.⁶ D-dimer levels were high in the patient group in our study, which is consistent with the literature. (D-dimer avg:2445(430-14540)). The death of four of fourteen acute stroke patients (29%) supports the situation associated with the aforementioned poor prognosis. COVID-19 infection increases the risk of stroke in patients with vascular risk factors, in addition to increasing the thrombotic process.

Cerebrovascular disease was seen in 5 (5.7%) of the patients in another study of 88 patients with severe COVID-19 infection. Cerebrovascular events were more common in those with risk factors including advanced age, hypertension, and diabetes, as well as those with high D-dimer levels.¹⁷

The main mechanisms of the thrombotic process due to COVID-19 are cytokine storm and immune system activation, embolic process secondary to pre-existing or new-onset arrhythmia, and ischemia secondary to hypoxia due to severe pulmonary involvement, thrombotic microangiopathy, endotheliopathy, and multifactorial activation of coagulation. The hypothesis that COVID-19 contributes to stroke risk depending on the severity of the disease is supported by the findings that those with severe disease have a higher risk of stroke (5.7%) and those with milder COVID-19 disease have fewer strokes. (0.8%).⁷

In conclusion, the multicyclic involvement of COVID-19 negatively affects prognosis. COVID-19 increases the risk of stroke in patients with multiple risk factors. In accordance with the literature, based on the results of our study, it can be said that close follow-up should be performed more carefully, especially in patients with pulmonary involvement and acute ischemic stroke, because mortality is likely to be higher in these patients. The limitations of our study are a retrospective study and increasing the number of patients' results would be more valuable.

Ethics Committee Approval: The approval of the Erciyes University Medical Faculty Ethics Committee was obtained (Date: 06.01.2021; Decision No: 2021/14) and additionally, and Turkish Ministry of Health approval was also obtained on the 19th of May 2020 for this study as required.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – RB, HA, ARB; Supervision – ARB, MG; Materials – GKÜ, ŞB; Data Collection and/or Processing – ŞB, GKÜ;

Analysis and/ or Interpretation – MG, HA; Writing– RB, ŞB, HA, MG.

Peer-review: Externally peer-reviewed.

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