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Clinical and laboratory characteristics of patients with COVID-19 followed up due to acute ischemic stroke

Dilek Yılmaz Okuyan, Meltem Karacan Gölen

Konya Numune State Hospital, Department of Neurology, Selcuklu, Konya, Turkey

ORCID ID of the author(s)
DYO: 0000-0003-0996-7739
MKG: 0000-0002-2422-9470

Corresponding Author
Dilek Yılmaz Okuyan
Konya Numune State Hospital, Department of Neurology, Hospital Street, No:22 Selcuklu, Konya, Turkey
E-mail: dilekyillmaz@gmail.com

Ethics Committee Approval
Approval was obtained from the Ethics Committee of Meram Faculty of Medicine, Konya Necmettin Erbakan University (20/11/2020, 2897) and the Ministry of Health for this retrospective study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: As coronavirus infectious disease 2019 (COVID-19) spreads worldwide, there is increasing evidence of an association between COVID-19 and vascular diseases. However, there are limited data on the clinical characteristics, stroke mechanisms, and prognosis of stroke patients with COVID-19. We aimed to evaluate the clinical and laboratory features and prognosis of patients with COVID-19 who were followed up due to acute ischemic stroke.

Methods: Fifty-six patients with a confirmed diagnosis of COVID-19 and acute ischemic stroke were included in this retrospective study. The demographic characteristics, medical history, symptoms, clinical, laboratory and imaging findings of the patients were evaluated retrospectively. The patients were divided into two groups according to the modified Rankin Scale (mRS) score in the first month, as those with good or poor prognosis.

Results: There were forty (71%) males, 16 (29%) females, and their overall mean age was 69.21 (8.77) (55-90) years. Fifty (89.2%) of 56 patients had pneumonia findings in chest computed tomography. The mortality rate was 35.7% (n=10) and 26 patients (46.4%) had a poor prognosis according to the mRS scores. Increased C-reactive protein and D-dimer levels were associated with mortality in the COVID-19 positive acute ischemic stroke patients (P=0.035, P=0.023).

Conclusion: The COVID-19–associated coagulopathy increases mortality and grossly affects the course of the infectious process. Inflammation markers may be associated with poor prognosis in stroke patients with COVID-19.

Keywords: COVID-19, SARS-CoV-2, Stroke, D-dimer, Mortality

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Introduction

Coronavirus infectious disease 2019 (COVID-19), caused by the new type of coronavirus 2 (SARS-CoV-2), leads to acute severe respiratory failure syndrome and has been spreading rapidly all over the world since December 2019. There is increasing evidence of an association between COVID-19 and cerebrovascular disease and other types of vascular disease [1].

In retrospective studies, the incidence of stroke in hospitalized COVID-19 patients ranges between 2.5% and 6%, with an increased frequency [2,3]. The clinical course of COVID-19 is more severe in older patients, male patients, patients with comorbidities such as hypertension, diabetes, heart disease and obesity, all of which are also considered as risk factors for stroke [4]. This increase in the incidence of stroke may be due to the increase in risk factors or to the progression of acute severe respiratory failure syndrome, multiple organ dysfunction syndrome, coagulopathy similar to that which occurs in sepsis, diffuse intravascular coagulation or cardiac effects in the process.

Many opinions can be put forward regarding the pathophysiologic mechanisms of stroke development in the course of COVID-19 infection. The uncontrollable cytokine storm seen in patients with severe infections can lead to multiple organ dysfunction. In particular, the activation of the microthrombotic pathway by destructive pathologic mechanisms mediated by the endothelial system can cause stroke. The markers of thrombosis tendency and inflammation such as D-dimer, fibrinogen, and C-reactive protein (CRP), and inflammatory cytokine levels such as tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2) receptor and IL-6 have been observed to increase in infected patients [5].

In post-mortem examinations of infected patients, lymphocytic endotheliitis was shown in many organs, including the lungs, heart, kidneys, small intestine, and liver, and ischemic events, due to direct endothelial damage and diffuse endothelial inflammation [6]. Two main pathways may be affected as a result of endothelial damage. Systemic inflammatory response syndrome (SIRS) can be triggered by cytokine release (e.g. IL-1, IL-6, TNF-α) and nitric oxide release as a result of inflammatory pathway activation. In the activation of the microthrombotic pathway, von Willebrand factor multimers (vWFM) are formed by platelet activation in the first stage. Non-destructible vWFMs cause formation of microthrombi together with activated thrombocytes in target organs. As a result, vascular microthrombotic disease develops due to endothelial damage [7].

It is thought that direct viral infection of endothelial cells through angiotensin-converting enzyme 2 (ACE-2) receptors may contribute to the host inflammatory response. Histopathologic analysis of the central nervous system (CNS) is required to determine whether the CNS vasculitis associated with SARS-CoV-2 within the wide clinical spectrum of COVID-19 can result from lymphocytic endotheliitis.

With the cytokine storm that also occurs in COVID-19, widespread microvascular thrombosis is observed with prothrombotic activation, and D-dimer levels are high in these patients [8]. Patients may also experience severe cardiac involvement leading to acute myocarditis and heart failure, which may be a risk factor especially for cardioembolic strokes [9]. In addition to these, severe hypoxia associated with acute respiratory distress syndrome developing during the course of COVID-19 negatively affects cerebral autoregulation, leading to intracerebral bleeding, cerebral vasodilation, and edema [10].

Given that there is a limited number of studies in the literature on acute ischemic stroke in patients with COVID-19, it is important to add case series to the literature. In this study, we aimed to evaluate the clinical and laboratory features and prognosis of patients with COVID-19 who were followed up due to acute ischemic stroke.

Materials and methods

Fifty-six patients with acute ischemic stroke and COVID-19 who were followed up between March and October 2020 in a pandemic hospital were included in this single-center retrospective study. All patients with COVID-19 were diagnosed according to the World Health Organization (WHO) guidelines, and patients who were positive for SARS-CoV-2 with real-time reverse transcription-polymerase chain reaction (rRT-PCR) in throat swabs were included.

The demographic features, medical history, symptoms, clinical, laboratory and imaging findings of the patients were evaluated from electronic medical records, retrospectively. The diagnosis of acute ischemic stroke was confirmed using brain computed tomography (CT), magnetic resonance imaging (MRI) and clinical symptoms. All neurologic symptoms were examined and approved by neurologists. Ischemic stroke types were classified according to the Trial of Org 10 172 in Acute Stroke Treatment (TOAST) classification [11]. The patients were divided into two groups according to modified Rankin Scale (mRS) scores in the first month as those having a good or poor prognosis. A mRS score of 3-6 was considered as poor prognosis. National Institute of Health Stroke Scale (NIHSS) scores were recorded at the time of admission. Patients were also grouped according to 30-day mortality.

Approval was obtained from the Local Ethics Committee (Protocol No: 2020-2897) and the Ministry of Health.

Statistical analysis

The normality of distribution of continuous variables was tested with the Shapiro-Wilk test. Student's t-test (for normal data) and the Mann-Whitney U test (for non-normal data) were used to compare two independent groups. The Chi-square test was used to investigate relationships between two categorical variables. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 24.0, and *P*-values <0.05 were considered statistically significant.

Results

Fifty-six patients with positive COVID-19 nasopharyngeal swab PCR tests who were followed up for acute ischemic stroke were included in this study. Forty (71%) of the patients were male, 16 (29%) were female, and the mean age was 69.21 (8.77) (55-90) years. The mean NIHSS score of the patients was 11.5 (1-24). Thirty-two (57.1%) patients had hypertension, 22 (39.3%) had diabetes mellitus, 10 (17.9) had atrial fibrillation, four (7.1%) had valvular heart disease, four

(7.1%) had a history of stroke, and 10 (17.9%) were smokers (Table 1).

Table 1: Demographic and clinical characteristics of patients with COVID-19 and acute ischemic stroke in the good and poor prognosis groups compared according to mRS scores

Characteristic	Total n=56	Good Prognosis (mRS 0-2) (n=26)	Poor Prognosis (mRS 3-6) (n=30)	*P*-Value
Demographics and risk factors				
Age, Mean	69.21(8.770)	70.54 (9.62)	68.07 (8.12)	0.467
Sex,-Males	40 (71.4%)	16 (61.5%)	24 (80%)	0.281
-Females	16 (28.6%)	10 (38.5%)	6 (20%)	
Current smoking	10 (17.9%)	4 (15.4%)	6 (20%)	0.339
Hypertension	32 (57.1%)	14 (53.8%)	18 (60%)	0.743
Diabetes mellitus	22 (39.3%)	8 (30.8%)	14 (46.7%)	0.390
Hyperlipidemia	18 (32.1%)	8 (30.8%)	10 (33.3%)	0.885
Atrial fibrillation	10 (17.9%)	4 (15.4%)	6 (20%)	0.755
Valvular heart disease	10 (17.9)	4 (15.4)	6 (20)	0.755
Previous stroke	4 (7.1%)	0 (0%)	4 (13.3%)	0.172
Stroke Classification (TOAST)	n (%)	n (%)	n (%)	
Large Vessel Disease	22 (39.3%)	12 (33.4%)	10 (50)	0.096
Small Vessel Disease	8 (14.3%)	8 (22.2%)	0 (0%)	
Cardio-Embolic	14 (25%)	6 (16.7%)	8 (40%)	
Stroke of Determined Origin	0 (0%)			
Stroke of Undetermined Origin	12 (21.4%)	10 (27.8%)	2 (10%)	
NIHSS on admission median	11.5 (8.04)	4.62 (3.55)	17.47 (5.63)	0.001*
Mortality, n(%)	20 (66.7)	0 (0 %)	20 (66.7 %)	0.001*

NIHSS: National Institute of Heath Stroke Scale, mRS: Modified Rankin Score

Lymphopenia was detected in 60.7% of the patients. CRP levels were increased in 89.2%, ferritin levels in 25%, D-dimer levels in 82.1%, lactate dehydrogenase (LDH) levels in 25%, and fibrinogen levels, in 32.1%. Thrombocytopenia was detected in 25%. No significant difference was observed between the good and poor prognosis groups in terms of laboratory parameters, but a statistically significant correlation was observed between mortality and increased CRP and D-dimer levels (P=0.035, P=0.023) (Table 2).

Table 2: Relationship between laboratory parameters and mortality in patients with COVID-19 and acute ischemic stroke

Laboratory Findings	30-day mortality		*P*-value
	No (n=18) Mean (SD)	Yes (n=10) Mean (SD)	
White blood cell, ×103/uL	8.48 (3.24)	11.27 (9.19)	0.851
Neutrophil, ×103/uL	6.81 (3.03)	7.5 (7.22)	0.556
Lymphocyte , ×103/uL	0.95 (0.43)	3.18 (6.83)	0.572
Monocyte, ×103/uL	0.69 (0.42)	0.59 (0.44)	0.410
Platelet ×103/uL	266.99 (118.91)	195.91 (66.1)	0.083
C-reactive protein (CRP), mg/L	80.71 (70.94)	90.9 (45.85)	0.035
Ferritin, ng/mL	416.61 (470.97)	501.61 (335.67)	0.609
D-dimer, ng/ml	1206.34 (1253.5)	7234.55 (12374.42)	0.023
Lactate Dehydrogenase (LDH), U/L	112.12 (333.8)	208.87 (274.06)	0.057
Fibrinogen, mg/dL	541.5 (119.78)	381.2 (210.44)	0.146
Prothrombin time (PT), s	13.58 (2.39)	14.68 (2.84)	0.230
Troponin, ng/mL	112.12 (333.8)	208.87 (274.06)	0.057

* Significant at 0.05 level, Student t or Mann Whitney u test

The median duration from the first symptoms of SARS-CoV-2 infection to acute ischemic stroke was 9 (range, 1-20) days. According to the TOAST classification, 22 of the 56 patients with ischemic stroke had large vessel atherosclerosis, eight had small vessel occlusion, and 14 had cardioembolism. The etiology was not clear in 12 patients (stroke of undetermined etiology).

Twenty-eight patients needed intensive care. The choice of treatment for ischemic stroke (antiaggregant / anticoagulant / i.v. tissue plasminogen activator) was determined by the treatment team, who comprehensively reviewed the clinical syndrome, laboratory findings, and time of presentation. Intravenous thrombolytic therapy was administered to five patients who had an acute ischemic stroke during hospitalization and mechanical thrombectomy was given to two patients. An anticoagulant dose of low-molecular-weight (LMW) heparin (enoxaparin) was administered to 10 patients with suspected cardioembolism, 42 patients received antiaggregants and deep vein thrombosis prophylaxis-dose enoxaparin.

There was evidence of pneumonia in the chest CTs of 50 (89.2%) patients. Mortality was observed in 20 patients (35.7%) and poor prognosis, in 26 patients (46.4%). Acute ischemic stroke was observed in 10 patients who were hospitalized for COVID-19 treatment, and 46 patients were hospitalized due to the association of acute ischemic stroke and COVID-19. There was a significant correlation between NIHSS scores at admission and mortality (P=0.001).

Discussion

Patients with severe symptoms of COVID-19 may be at risk for thromboembolic events resulting from COVID-19-associated coagulopathy. SARS-CoV-2 can damage endothelial cells and activate inflammatory and thrombotic pathways [6]. Endothelial cell infection or monocyte activation, upregulation of tissue factors, and the release of microparticles that activate the thrombotic pathway and cause microangiopathy are also valid for SARS-CoV-2, as in other viruses [12, 13]. It is suggested that monocyte activation forms part of the secondary hemophagocytic lymphohistiocytosis identified in severe COVID-19 [14]. Endothelial dysfunction can lead to microvascular and macrovascular complications in the brain, as well as in systemic events [15].

Studies reported that patients hospitalized due to COVID-19 showed increased coagulation activity with increased D-dimer concentrations [16,17]. In a retrospective study, D-dimer levels were higher in patients with cerebrovascular disease and COVID-19 than patients with COVID-19 without cerebrovascular disease [18]. In our study, D-dimer levels were higher among the non-survivors (p = 0.023). In a case series of 221 patients with COVID-19 published by Li et al., 11 patients had acute ischemic stroke, one patient had sinus vein thrombosis, and one patient had hemorrhagic stroke (15). Thrombocytopenia increased fibrinogen, and D-dimer levels in these patients were associated with a coagulopathy secondary to COVID-19.

Ischemic infarction areas seen in COVID-19 tend to occur in large vessel territories, and more often in multiple vessel territories [19]. In this study, 36 of 56 patients had large vessel atherosclerosis, 14 had small vessel occlusion and 18 had cardioembolism. In New York City, five stroke patients with COVID-19 who were aged under 50 years had large vessel occlusion (mean NIHSS: 17) [20]. This case series suggested that young patients might also be at risk for ischemic stroke. In our case series, there were no patients aged under 50 years.

A pro-inflammatory immune response develops during COVID-19 and the cytokine storm that develops in some patients gets ahead of the damage caused by the infection. Hypercoagulability is such an example [21]. Coexistence of COVID-19 with a severe headache and cerebral sinus vein thrombosis was reported in a 59-year-old patient with a history of obesity, smoking, hypertension, and diabetes [3]. Sinus vein thrombosis was not encountered in our case series.

In a study involving 184 COVID-19 patients in an intensive care unit (ICU) in Germany, the incidence of thrombosis was 31%, and arterial ischemic cerebrovascular disease was found in three patients. It is recommended that thrombosis prophylaxis should be strictly administered in all

patients with COVID-19 admitted to the ICU [22]. In our study, LMW heparin prophylaxis was given to all patients.

In a multivariate analysis of a retrospective series of 440 patients with severe COVID-19, age, prolongation of prothrombin time, increased D-dimer, and thrombocytopenia were associated with mortality [23]. In our study, mortality was correlated with high CRP and D-dimer levels and thrombocytopenia, but no significant difference was found in terms of age and other variables. In our study, 40 (71%) of 56 patients had severe COVID-19 pneumonia findings, which suggested that the possibility of acute ischemic stroke was higher in patients with severe infections, similar to the literature [24].

Limitations

This study had some limitations. It was a single-center study. We had a limited number of patients and we were not able to perform advanced etiologic examinations in every patient. However, it may be beneficial to share our clinical experience because there are a limited number of small case series studies on acute ischemic stroke in COVID-19. More data are needed in this area to determine the contribution of processes involved in the pathogenesis of stroke in patients with COVID-19. Multicenter clinical studies with a larger number of patients are needed.

Conclusion

Acute ischemic stroke is not uncommon in patients with COVID-19, particularly those who are severely infected and those with pre-existing vascular risk factors. COVID-19–associated coagulopathy increases mortality and has important effects on the course of the infectious process. Inflammation markers may be associated with poor prognosis in patients with stroke and COVID-19. However, the data in the literature are limited. In this period, the accumulation of knowledge, which will increase with the meticulous monitoring and recording of patients with a multi-faceted perspective, will contribute to understanding the underlying pathophysiologic mechanisms and determining the appropriate clinical approach.

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