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Stroke Mechanism in COVID-19 Infection: A Prospective Case-Control Study

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Background: The characteristics and pathophysiological mechanisms involved in acute ischemic stroke in patients with COVID-19 infection have not been fully clarified. We prospectively studied the phenotypic and etiological features of acute stroke occurring in COVID-19 infection. *Patients & methods:* Within nine months starting from April-2020, the presence of COVID-19 infection was determined by thoracic CT and SARS-CoV-2 PCR in all acute stroke cases managed in a single tertiary center. Consecutive and prospective data on vascular risk factors/comorbidities, in-hospital quality metrics, discharge outcomes, etiological subclassification and blood markers of thrombosis / inflammation were compared in 44 COVID-19 positive cases (37 acute ischemic stroke, 5 TIA, 2 intracerebral hematoma) and 509 COVID-19 negative patients (355 ischemic, 105 TIA, 44 hematoma and 5 stroke mimic). *Results:* COVID-19 positive patients had more severe strokes, delayed hospital admission, longer hospital stay, higher mortality rates, but had similar vascular risk factors/comorbidities frequency, thrombolysis/thrombectomy utilization rates, metrics, and stroke etiological subtype. They had significantly higher CRP, fibrinogen, ferritin, leukocyte count and lower lymphocyte count. No difference was detected in aPTT, INR, D-dimer, platelet, hemoglobin, homocysteine levels and ANA, anti-dsDNA antibody and ENA panel positivity rates. Anti-phospholipid antibodies have been studied in 70% of COVID-19 positive and all cryptogenic patients, but were never found positive. Tests for coagulation factor levels and hereditary thrombophilia did not show major thrombophilia in any of the stroke patients with COVID-19. *Conclusion:* We documented that there is no significant difference in etiological spectrum in acute stroke patients with COVID-19 infection. In addition, cryptogenic stroke and antiphospholipid antibody positivity rates did not increase.

Key Words: COVID-19—Viral pneumonia—Anticoagulation—Stroke—Intracerebral hemorrhage—Transient ischemic attack

Introduction

Many critical differences have been observed in the epidemiology and management of collateral diseases such as acute stroke during the "coronavirus disease 2019" (COVID-19) pandemic that has deeply affected our daily lives for more than a year. The increase in stroke rate associated with COVID-19 infection reported in the first wave was not supported in most of the subsequent studies.[1,2] Differences, if any, in phenotype, underlying mechanisms and treatment responses of acute stroke in "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" positive patients remained scarcely clarified until now.[2] In addition, the role of SARS-CoV-2 induced coagulopathy and thromboinflammation in the stroke mechanism is still a matter of debate.[1]

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In this study, we report the phenotypic characteristics along with inflammatory and coagulation profile of acute stroke occurring in the setting of COVID-19 disease in a relatively large and homogenous cases series.

Patients and methods

A total 554 consecutive acute stroke patients hospitalized at Hacettepe University hospitals between 16.4.2020 and 14.1.2021 were prospectively included in this study. The study protocol was approved by the non-interventional ethics committee of Hacettepe University, and the relevant committee of the Turkish Ministry of Health; database registration consent [for details see reference #3[3]] was obtained from all patients or their representatives.

As part of the hospital inpatient admission policy, real time reverse transcriptase polymerase chain reaction (RT PCR) for the SARS-CoV-2 virus was tested on the first day of presentation to the hospital and then when needed. WHO clinical progression scale was determined for each PCR positive patient.[4] Low-dose thorax computed tomography (CT) were obtained in all acute patients on emergency basis as per hospital policy and the Turkish expert opinion.[5]

The clinical severity of stroke was quantified by National Institutes of Health Stroke Scale (NIHSS) at admission, 24 hours, and at discharge.[6] Pre-morbid and discharge functional status was assessed using the modified Rankin scale (mRS).[7] A mRS less than 3 was defined as "good or favorable clinical outcome", and "0 or 1" as an "no/minimal disability". The Causative Classification of Stroke algorithm was used for etiological classification of stroke.[8]

Admission erythrocyte sedimentation rate, complete blood count (platelet $x10^3/\mu L$, normal range, 156−373), hemoglobin (g/dL, normal range, 13.6−17.2), leukocyte ($x10^3/\mu L$, normal range, 4.3−10.3), lymphocyte ($x10^3/\mu L$, normal range, 1.3−3.5), C reactive protein (CRP, mg/dL, normal range, 0-0.8), activated partial thromboplastin time (aPTT, normal range, 22.5−32 s), prothrombin time (PT, normal range, 10.4−12.6 s) and International Normalized Ratio (INR, normal range, 0.8−1.2), procalcitonin (ηg/mL, normal range, 0−0.1), D-dimer (mg/L, normal range, 0−0.55), fibrinogen (mg/dL, normal range, 180−350), homocysteine (μmol/L, normal range <15), ferritin (μmol/L, normal ranges 11−336) were studied in all patients. Antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), extractable nuclear antigen (ENA) panel, antiphospholipid antibodies including lupus anticoagulant (30−38 s, with dRVVT-Dilute Russell's viper venom time), anticardiolipin antibodies (IgG, normal range, 0−12 GPL/mL and IgM, normal range, 0−12 MPL/mL) and beta 2 glycoprotein-I (IgG and IgM, RU/mL, normal range <20), Factor VIII / V / X / XIII levels (as percent), genetic analyses for common hereditary thrombophilias (Factor V Leiden, Prothrombin G20210A, Methylenetetrahydrofolate reductase (MTHFR) A1298C and C677T polymorphism, Plasminogen activator inhibitor-1 (PAI-1) polymorphism) were studied in selected cases.

Statistics

Comparisons between groups such as COVID-19 positive and negative acute stroke cases, were performed using Pearson's Chi Square, Fisher's Exact and its Freeman-Halton extension tests, and Kruskal-Wallis test for categorical variables, and Student's t, Mann-Whitney *U* and ANOVA for continuous variables. Distribution normality was tested by Kolmogorov-Smirnov or Shapiro-Wilk tests as appropriate. Multivariable logistic regression models were constructed to search the association between COVID-19 infection and different stroke characteristics including outcomes. Logistic regression models were adjusted for variables with $p < 0.1$ in univariate analyses. All statistical analyses were performed using SPSS version 22. $P < 0.05$ was set as the threshold for statistical significance.

Results

Characteristics of COVID-19 positive cases

Seventeen of 44 cases diagnosed with COVID-19 infection were PCR and thorax CT positive, 8 cases were PCR positive and thorax CT negative, and 19 cases were PCR negative but thorax CT positive. In 6 patients in the latter group, the antibody test performed later was found to be positive in four cases. 40 (91%) of these patients were hospitalized for two or more days. Thirty-three (75%) patients had a "mild" degree of COVID-19, and 19 of them required oxygen by mask or nasal prongs at the time of stroke occurrence. While non-invasive mechanical ventilation (NIVM) or high flow oxygen therapy (HFOT) was applied in six of the 11 (25%) patients in the severe category, 5 patients were intubated and invasive mechanical ventilation (IMV) was applied.

Ischemic stroke

There were a total of 355 COVID-19 negative and 37 COVID-19 positive ischemic stroke patients. Of these, 276 (78%) PCR negative and 34 (92%) PCR positive cases were hospitalized in our center, and the remaining were either transferred to other centers or managed at home (*Supplementary* Fig. 1).

While male and active smoker ratio was lower in COVID-19 positive strokes, no significant difference was found in terms of the frequency of vascular risk factors. In COVID-19 positive cases, the clinical severity of stroke (NIHSS) was significantly higher, and symptom onset to hospital admission interval was significantly longer (approximately 1000 minutes later, Table 1).

Table 1. *Clinical characteristics of patients with acute ischemic stroke.*

		COVID-19 (+)	COVID-19 (-)	
n		37	355	p
Demographics & past medical history				
Mean age		70±15	70±15	0.946
Female		17%	50%	<0.001
Hypertension		68%	71%	0.691
Diabetes mellitus		43%	32%	0.149
Dyslipidemia		8%	14%	0.293
Coronary heart disease		30%	36%	0.464
Congestive heart disease		8%	14%	0.312
Atrial fibrillation (at admission)		8%	16%	0.229
Atrial fibrillation (detected during hospital stay)		19%	15%	0.489
Smoking (active)		6%	22%	0.017
Alcohol		0%	5%	0.161
Previous stroke		22%	24%	0.780
Stroke characteristics & treatment				
NIHSS admission		12± 7	9±8	0.034
NIHSS 24th hour		11±7	8±8	0.064
NIHSS at discharge		6±7	7±7	0.737
Symptom onset-to-door time (minute)		2145±3852	1084± 2375	0.016
IV tPA use		10.8%	7.6%	0.492
IV tPA (door-to-needle time) (minute)		127±31	121±39	0.801
Mechanical thrombectomy use		8.1%	16.3%	0.189
MT (Door-to-groin puncture time) (minute)		162±34	208±57	0.189
Hospitalized		92%	78%	0.084
ICU care		76%	50%	0.003
Invasive mechanical ventilation		60%	25%	<0.001
Heparin	Any	73%	62%	0.150
	Intravenous	19%	36%	0.045
	Subcutaneous	16%	3%	0.003
	Low molecular weight	38%	23%	0.042
Aspirin		41%	47%	0.431
Clopidogrel		16%	22%	0.417
In-hospital metrics				
Brain computed tomography		95%	98%	0.184
Cervicocranial tomographic angiography		65%	88%	<0.001
Brain magnetic resonance imaging		89%	93%	0.363
Cranio(±cervical) magnetic resonance angiography		63%	67%	0.598
Transthoracic echocardiography		14%	60%	<0.001
Stroke etiology (CCS)				
Cardioembolism		40%	34%	0.081
Largery artery disease		22%	22%	
Small artery disease		16%	10%	
Cryptogenic other		16%	7%	
Cryptogenic embolism		3%	10%	
Uncommon		0%	6%	
Undetermined		3%	11%	
Outcome				
Median modified Rankin scale		6±4	3±3	<0.001
Median modified Rankin scale in survived		2±3	3±2	0.143
modified Rankin scale≤2		24%	45%	0.014
Mortality		54%	8%	<0.001
Median of length of stay in hospital (days)		11±14	5±13	0.002
Median of length of stay in hospital (in survived, days)		10±45	5±12	0.223

Abbreviations: CCS: Causative Classification of Stroke; ICU: Intensive Care Unit; IV tPA: Intravenous tissue-type plasminogen activator; MT: Mechanical Thrombectomy; NIHSS: The National Institutes of Health Stroke Scale.

No difference was found in the rates of systemic thrombolytic use (10.8% vs 7.6%, $p = 0.492$ for COVID-19 positive and negative, respectively) and thrombectomy (8.1% vs 16.3%, $p = 0.189$). Intensive care admission and mechanical ventilation use were significantly higher in cases with COVID-19, as expected. The overall anticoagulant use rate was not significantly different in COVID-19 cases. Physicians involved in stroke cases with COVID-19 preferred subcutaneous unfractionated or low molecular weight heparin over intravenous heparin. (Table 1).

In all of the patients with COVID-19 infection, at least one cervico-cranial angiography (either CT or MR angiography) was performed, but if one of them was done, the other was usually not obtained. CT angiography appears to be less preferred in this situation. Transthoracic echocardiography was performed significantly less frequently in SARS-CoV-2 positive cases.

Stroke etiological sub-classification did not indicate a difference in patients with COVID-19 ($p = 0.081$). Both groups had cardioembolism (40% in COVID-19 positive and 34% in COVID-19 negative) as the most prevalent etiological category. Other cryptogenic category was numerically higher in the COVID-19 positive group (Table 1).

Acute stroke patients diagnosed as having COVID-19 were hospitalized for about 2 times longer (Table 1). Mortality rate was obviously higher in stroke patients with COVID-19 (54% vs 8%, OR = 16.5, 95%CI, 7.1−38.3, adjusted for NIHSS and age, $p < 0.001$). The good prognosis rate at discharge was also significantly lower (24% vs 45%, OR = 0.39, 95%CI, 0.18−0.85, $p = 0.014$). However, when adjusting for NIHSS (OR = 0.79, 95%CI, 0.75−0.83, $p < 0.001$) and age (OR = 0.97, 95%CI, 0.95−0.99, $p = 0.002$, per 1 year), having COVID-19 did not significantly decrease the good prognosis rate (OR = 0.56, 95%CI 0.22−1.44, $p = 0.228$). There was no difference in the minimal / no disability rate in terms of having COVID-19 infection (16% vs 15%, $p = 0.761$). IV tPA was given to 4 SARS-CoV-2 positive cases. One patient died of systemic causes, one was discharged with mRS 1 and two as mRS 3. Three patients who underwent thrombectomy died due to systemic reasons albeit excellent procedure success (*Supplementary* Table 1).

Coagulation and inflammation profile

C-reactive protein, erythrocyte sedimentation rate, fibrinogen and ferritin levels were significantly higher in COVID-19 (+) hospitalized ischemic stroke cases. Lymphocyte count was significantly lower and leukocyte count was significantly higher. Procalcitonin levels showed a numerical elevation (Table 2). No difference was observed between SARS-CoV-2 positive and negative patients in terms of hematological markers such as activated partial thromboplastin time, INR, D-dimer, platelet, hemoglobin and homocysteine levels.

Anti Nuclear Antigen, anti-dsDNA antibody and ENA panel positivity rates were not different in COVID-19 stroke cases. While the ANA titer was 1/100 in 9 COVID-19 positive cases and 1/320 in one, it was 1/100 in 10 cases, 1/160 in one case and 1/320 in two cases in the COVID-19 negative group. Anti-phospholipid antibodies including lupus anticoagulant, anti-cardiolipin antibodies and beta-2 glycoprotein 1 were studied in more than 70% of the acute stroke COVID-19 positive patients and in all of the cryptogenic cases but were never found to be positive (Table 2).

Coagulation factor levels could be studied in a small number of patients, but there was no sign that there might be a significant difference between the two groups. Hereditary thrombophilia was studied in 56% of SARS-CoV-2 (+) cases and in the entire cryptogenic COVID-19 stroke group. Factor V Leiden and prothrombin G20210A mutation homozygous form were not detected in the study group. No difference was found in SARS-CoV-2-positive cases in terms of heterozygosity. The distribution of polymorphism in MTHFR C677T, MTHFR A1298C and PAI-1 gene also did not differ in the COVID-19 positive stroke group (Table 2).

Transient ischemic attack

There were a total of 110 cases diagnosed with TIA. Five percent of these were SARS-CoV-2 PCR positive. Only 36 (33%) of the cases could be hospitalized. Others were referred to either the stroke outpatient clinics or other centers (*Supplementary* figure 1). The basic characteristics of 4 COVID-19 positive (OMS score 4 in one and 5 in three) and 32 SARS-CoV-2 negative hospitalized cases were documented in the *supplementary* table-2. In the COVID-19 positive group, one case was classified as large artery disease and 3 cases as cryptogenic, and in the COVID-19 negative group, 10 cases were classified as cryptogenic, 8 cases as large artery disease, 4 cases as cardioembolism, 4 cases as other uncommon and 6 cases as undetermined.

Intracerebral hematoma

A total of 46 (9%) were diagnosed with acute intracerebral hemorrhage. 2 patients were positive for SARS-CoV-2 PCR. 32 (70%) patients were hospitalized, the remaining 14 patients were referred from the emergency service to other centers (*Supplementary* figure 1). The clinical and laboratory data of the groups are provided in detail in the *supplementary* table-3. In SARS-CoV-2 (+) cases, one of the intracerebral hemorrhages was caused by warfarin overdose and the other was of hypertensive type. Two patients were treated in the intensive care unit and one passed away.

Discussion

We herein describe the clinical and etiological features of stroke in patients who are positive for COVID-19. This is the first prospective study data presented from Turkey. Our ischemic stroke patients were of similar age to

Table 2. *Blood markers in hospitalized patients with acute ischemic stroke.*

		COVID-19 (+)	COVID-19 (-)	
N		37	355	P
Blood markers (studied in all)				
C-reactive protein		9.32±9.96	3.93±7.31	<0.001
Procalcitonin		4.51±16.89	1.24±7.78	0.054
Erythrocyte sedimentation rate		40±29	25±22	0.001
Activated partial thromboplastin time		25.49±5.23	26.29±16.2	0.765
Prothrombin time (as INR)		1.31±0.41	1.17±0.41	0.055
D-dimer		5.27±6.58	4.33±10.04	0.585
Fibrinogen		460±186	365±140	0.005
Ferritin		456±497	158±683	0.015
Platelet		229±101	229±101	0.701
Hemoglobin		12.16±2.84	12.93±2.38	0.067
Lymphocyte count		1.09±0.68	1.81±1.15	<0.001
Leukocyte count		10.81±3.7	9.36±4.07	0.039
Homocysteine		19.4±9.05	15.9±10.65	0.121
Blood markers (studied in selected cases)				
Anti Nuclear Antigen	Studied	70%	12%	
	Positive	42%	34%	0.721
Anti-dsDNA Antibody	Studied	70%	11%	
	Positive	0%	6%	0.221
ENA Panel	Studied	70%	11%	
	Positive	0%	0%	-
Anti-phospholipid antibody	Studied	70%	26%	
	Positive	0%	17%	0.023
Factor V Leiden	Studied	56%	6.5%	
	Heterozygous	10%	9%	0.957
Prothrombin G20210A mutation	Studied	56%	7.2%	
	Heterozygous	0%	12%	0.148
MTHFR C677T polymorphism	Studied	56%	7.2%	
	Heterozygous	29%	52%	0.076
	Homozygous	10%	0%	
MTHFR A1298C polymorphism	Studied	56%	7.2%	
	Heterozygous	24%	39%	0.206
	Homozygous	0%	6%	
PAI-1 gene polymorphism	Studied	56%	7.2%	
	Heterozygous	19%	40%	0.002
	Homozygous	5%	27%	
	4G/4G	38%	30%	0.780
	4G/5G	19%	46%	
	5G/5G	43%	24%	
Factor VIII	Studied	26%	26%	
	Average	265±135	248±91	
Factor V	Studied	21%	5%	
	Average	109±16	105±18	
FactorX	Studied	21%	5%	
	Average	76±25	94±28	
FactorXIII	Studied	21%	5%	
	Average	87±23	99±33	

Abbreviations: MTHFR: Methylenetetrahydrofolate reductase; PAI: Plasminogen activator inhibitor.

contemporary controls. The issue of interplay between age, COVID-19 infection and stroke risk has not been clarified yet. While the COVID-19 positive patients are older in some prior series,[9] they were found to be younger in others.[10] The frequency of male was higher in our series. While no gender difference was detected in some studies,[9] male dominance was also found in others.[11] Increase of stroke incidence may be related to the more frequent or severe course of the disease in men.[12] Unlike some of the previous studies[9], we found that vascular risk and comorbidity profile in COVID-positive stroke cohort was not significantly different from COVID-negative ones. A

lower prevalence of smoking that we noted was noted in several prior studies without apparent reason.[11,13]

We have confirmed that the clinical picture of COVID-positive stroke cases is more severe (such as high NIHSS, high rate of ICU admission and mechanical ventilation).[9–11,13] In COVID-19 positive cases, the interval between symptom-onset and arrival to the hospital was longer. In other words, COVID (+) patients arrived later. Reasons for this delay may involve symptom scanning and notification to central transfer system by the emergency medical service in the pre-hospital setting. Among the causes of high stroke severity observed in COVID-19 cases, neurological examination deterioration due to infection can be encountered. Other causes can include a tendency to large artery occlusion and the clinical progression already due to late arrival.

We found no difference in terms of in-hospital time metrics such as door-to-needle or door-to-groin time in contrast to 15−25 min of prolongation in these metrics has been reported in the literature[10]. We applied IV tPA in a total of four COVID-19 (+) patients and interventional therapy in three patients. Although the immediate results of the interventional procedure were very good in all three patients, we could not prevent death due to severe systemic diseases. Due to limited number of patients treated we cannot make any further comments on the success of acute stroke treatment in the settings of COVID-19 infection. Possibly, multi-national registries or meta-analysis will be able to produce solutions in this regard. The data collected so far suggests that it is not reasonable to expect a change in the benefit of recanalization therapies.[10,14]

When compared to SARS-CoV-2-negative stroke patients, SARS-CoV-2-positive stroke patients were found to have higher mortality rates, worse functional outcomes at discharge and longer duration of hospitalization.[2,9-11,13] Our data supported the finding of increased mortality rate, but we could not document presence of COVID-19 infection as an independent predictor of functional prognosis after adjustment by age and NIHSS.

We found that the rate of cryptogenic stroke did not increase in SARS-CoV-2 positive cases. Our cryptogenic stroke rate was approximately one-fifth, but rates of up to two-thirds were reported in the literature.[13,15] The reason for this excess may be the possibility of COVID-19-specific stroke, as well as the inability to transfer from the ICU to examination suites due to the severity of the pulmonary disease, or the refusal to perform close contact tests such as transthoracic echocardiography. In our study, the rate of transthoracic echocardiography was also low, but this was compensated by long-term bedside cardiac monitoring and at least one cervicocranial angiography for each patient. Our data suggest that there is no type of ischemic stroke unique to COVID-19, or at least not very common.

Supporting the literature data, we found that acute phase reactants such as CRP, erythrocyte sedimentation rate and fibrinogen and disease severity markers such as ferritin were higher in the COVID-19 group. In addition, as expected lower lymphocytes and higher leukocytes counts was remarkable in COVID-19 patients.

In the hypercoagulable panels we tested on the day of stroke, we did not detect any changes specific to COVID-19 patients. In particular, the antiphospholipid antibodies we measured in more than two-thirds of the patients and in all of the cryptogenic cases did not come out as positive in any of the COVID 19 positive cases. In the literature, SARS-CoV-2 infection and antiphospholipid antibody positivity have been debated since the beginning of the pandemic.[16,17] In the light of the data added later, we can formulate the connection of antiphospholipid antibodies with COVID-19 infection as follows: The presence of antiphospholipid antibodies in catastrophic COVID-19 infection may contribute to arterial and venous thromboembolic events.[18] Apart from that, the prevalence of these antibodies is low in COVID-19. If it is found to be positive, it is almost always in low titer and transient. In most cases, this is an epiphenomenon not precipitating vascular thrombotic events.[19]

Our study is not devoid of limitations: Having a single center and a limited number of patients is a limitation. Especially the number of TIA and intracerebral hemorrhage cases and the number of patients for whom IV tPA and interventional treatment were administered were low. But, we have presented these data so that it can be used in data combination. As a result, we added new findings on etiology, prognosis and thromboinflammation within the scope of COVID-19 infection and ischemic stroke connection. Stroke and COVID-19 infection association will continue to be studied.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105919.

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