

Cardioembolic stroke, the most common subtype of stroke in COVID 19: A single center experience from Isfahan, Iran

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Background: Some studies showed the cerebrovascular manifestation in patients with recently pandemic coronavirus 2 named the coronavirus disease 2019 (COVID-19). However, there are rare reports about stroke subtypes in these patients. Here, we reported the stroke subtype in patients with laboratory-confirmed diagnosis of COVID-19 and treated at our hospitals, which are located in Isfahan, Iran. **Materials and Methods:** This is a retrospective, observational case series. Data were collected from March 01, 2020, to May 20, 2020, at three designated special care centers for COVID-19 of Isfahan University of Medical Sciences. The study included 1188 consecutive hospitalized patients with laboratory-confirmed diagnosis of COVID-19. **Results:** Of 1188 COVID-19 patients, 7 (0.5%) patients developed stroke. Five (0.4%) had ischemic arterial stroke, 1 (0.08%) hemorrhagic stroke and 1(0.08 %) cerebral venous and sinus thrombosis. Sixty percent of ischemic stroke were cardioembolic stroke (CE) and the rest 2 (40%) were embolic stroke of undetermined source. Three male patients (40%) had stroke as a presenting and admitted symptom of COVID-19. Four patients (57%) had severe COVID-19. **Conclusion:** Stroke was an uncommon manifestation in COVID-19 patients. CE was a common subtype of stroke in COVID-19 patients in our centers.

Key words: COVID-19, embolic stroke, infection, stroke

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INTRODUCTION

Coronavirus disease 2019 (COVID 19) has multiple neurological manifestations including stroke.^[1] Acute stroke has been reported to be one of the uncommon presentations in COVID-19 patients with an incidence of 1%–6%.^[1-5] The consequent imbalance in vasodilation, neuroinflammation, oxidative stress, and thrombogenesis is thought to be the underlying mechanism for stroke pathophysiology during COVID-19.^[6] As the data on stroke and COVID-19 are emerging, there is a rare report regarding the subtype of stroke in this population. Here, we report the stroke subtype of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 1188 patients

with laboratory-confirmed diagnosis of COVID-19 and treated at our hospitals, which are located in Isfahan, Iran.

METHODS

Study design and participants

This retrospective, observational study was done at three centers (Khorshid Hospital, Alzahra Hospital, and Kashani hospital) of Isfahan University of Medical Science (IUMS) in Isfahan, Iran. These three centers are designated hospitals assigned by the government to treat patients with COVID-19. We retrospectively analyzed consecutive patients from March 01, 2020, to May 20, 2020, who had been diagnosed as having COVID-19,

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according to the World Health Organization (WHO) interim guidance.^[7]

Assays for COVID-19 were completed in accordance with standards recognized by the WHO. A confirmed case of COVID-19 was defined as a positive result on high amount sequencing or real-time reverse transcription–polymerase chain reaction analysis using a sample obtained through a nasopharyngeal swab.^[7]

According to the clinical care needs, radiologic assessments included chest and head computed tomography (CT), and all laboratory testing (a complete blood cell count, blood chemical analysis, coagulation testing, assessment of liver and renal function testing, C-reactive protein, creatine kinase, and lactate dehydrogenase) was performed. One thousand one hundred and eighty-eight hospitalized patients with laboratory confirmation of SARS-CoV-2 were included in the analysis.

Before enrollment, verbal consent was obtained from patients or a relative for patients who could not give consent. The study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of IUMS on March 01, 2020 (Ethical code: IR.MUI.MED.REC.1399.202).

Data collection

We used all medical records, nursing records, laboratory findings, and radiologic evaluations for all patients with laboratory-confirmed SARS-CoV-2 infection. All epidemiologic data on age, sex, comorbidities (hypertension, diabetes, smoking, opium addiction, cardiac or cerebrovascular disease, malignancy, and chronic kidney disease), typical symptoms from onset to hospital admission (fever, cough, anorexia, diarrhea, throat pain, and abdominal pain), nervous system symptoms, laboratory findings, and CT scan (chest and head if available) were also included.

Subjective symptoms were afforded by patients who were conscious, cognitively and mentally normal, and linguistically capable to respond to interview. Any missing or uncertain records were clarified through direct communication with involved patients, health-care clinicians, and their families. We defined the degree of severity of COVID-19 (severe vs. nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.^[8]

All consecutive patients with clinical confirmation of stroke syndrome in neurological consultation during this time frame were included. All stroke diagnoses were reviewed and confirmed by two trained stroke

neurologists. Major difference between two reviewers was resolved by consultation with a third reviewer. Stroke subtype and diagnosis were according to the TOAST criteria.^[9] Acute ischemic stroke (AIS) patients underwent a standard diagnostic evaluation, including brain CT scan and magnetic resonance imaging (MRI) imaging, intracranial and extracranial vascular imaging, and cardiac evaluation, including electrocardiogram (ECG), continuous cardiac telemetry for at least 24 h, and transthoracic echocardiography. We also included embolic stroke of undetermined source (ESUS) as nonlacunar cryptogenic ischemic strokes in whom embolism was the likely stroke mechanism.^[10] Baseline characteristics of stroke patients, type of stroke, Modified Rankin Scale (MRS)^[11] at discharge, risk factors for stroke, medications, the National Institutes of Health Stroke Scale/Score, time to presentation – hr, sign and symptom of stroke, vascular territory, imaging for diagnosis of stroke, treatment for stroke, echocardiography findings, ECG findings, cervical and cerebral vessel investigation, and COVID-19 symptoms were recorded. We also followed the patients after 1 month with telephone interview, and the prognosis according to MRS was recorded.

RESULTS

Among 1188 COVID-19 patients during March 01, 2020, to May 20, 2020, 7 (0.58%) patients developed stroke [Table 1]. Three patients from all COVID-19 (0.25%) had stroke as a presenting symptom of COVID-19. Four from seven stroke patients (57%) had severe COVID-19 manifestation and developed stroke during hospitalization. The average time of onset of stroke after COVID-19 diagnosis was 6.7 days. Of seven patients with acute stroke, five from all COVID-19 (0.42%) and five from seven stroke patients (71.4%) were ischemic arterial stroke, one (0.08%) was hemorrhagic stroke, and one (0.08%) was found to have cerebral venous and sinus thrombosis as the etiology of stroke. The etiology of ischemic stroke was cardioembolic stroke (CE) in three patients from five ischemic stroke patients (60%) and ESUS in two patients (40%). The mortality rate was 40% among stroke patients. Table 1 shows the clinical characteristics of seven stroke patients with COVID-19.

DISCUSSION

In this study, we showed that the incidence of stroke in COVID patients was not too high and the most frequent type was AIS. Among the AIS patients, the most stroke subtype was CS.

We showed low frequency (0.5%) of cerebrovascular disease in COVID-19 patients. It was in contrary of reports from China that was nearly to 5%.^[1] However, recent studies, similar to our study, showed low frequency (1%–2%)

Table 1: Clinical characteristic of seven stroke patients with coronavirus disease 2019

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patients 7
Age (years)	74	70	65	63	78	81	61
Sex	Male	Male	Male	Male	Male	Male	Male
Stroke subtype	Cardioembolic	Embolic stroke undetermined source	Cardioembolic	Cerebral venous and sinus thrombosis	Embolic stroke undetermined source	Cardioembolic	Subarachnoid hemorrhage
Medical history and risk factors for stroke	Hypertension, diabetes mellitus, end-stage renal disease	Hypertension, diabetes mellitus	New arterial fibrillation	Epilepsy, coronary artery disease	Hypertension, cerebrovascular accident 1 year before	New acute myocardial infarction, hypertension	Hypertension
Medications	Furosemide, valsartan, metoprolol, amlodipine, Lantus insulin, warfarin	Metformin, losartan	Warfarin, amlodipine	Clonazepam, tamsulosin, valproic acid, levetiracetam, gabapentin, citalopram, quetiapine, warfarin	Losartan, amlodipine, aspirin, metoprolol, colchicine, rivaroxaban	Losartan, warfarin	Nimodipine
NIHSS* score on admission	21	18	16	10	8	18	18
MRS* at discharge	6 (died)	4	4	2	2	6 (died)	4
MRS after 1 month	Died	3	3	1	2	Died	4 (yet admitted)
Time to the presentation (h)	10	13	7	On the day of admission	7	On the day of admission	On the day of admission
Signs and symptoms of stroke	Dysphagia, quadriplegia, loss of consciousness	Broca's aphasia, hemiparesis	Wernicke aphasia, hemiparesis	Broca's Aphasia, mild hemiparesis	Dysarthria, hemiparesis	Global aphasia, hemiparesis	Loss of consciousness
Vascular territory	The right posterior cerebral artery territory (hemorrhagic part in infarction area)	The right posterior cerebral artery territory	Superior division of Right middle cerebral artery	left transverse sinus thrombosis	Paramedian artery	Left middle cerebral artery M1 segment	Anterior communicating aneurysm
Imaging for diagnosis	CT	CT and MRI	CT	CT, MRI, MRV	CT and MRI	CT and MRI	CT, CTA, digital subtraction angiography
Treatment for stroke	Anticoagulant	Antiplatelet (prophylactic dose)	Anticoagulant	Anticoagulant	Antiplatelet (prophylactic dose) t	Anticoagulant	Aneurysm coiling
Echocardiography	Ejection fraction <30%	Ejection fraction 50%, mild MR, mild TR	Ejection fraction 50%	Not done	Ejection fraction 60%	Ejection fraction <30%	Not done
ECG	Sinus rhythm	Sinus rhythm	Atrial fibrillation	Sinus rhythm	Sinus rhythm	Sinus rhythm	Sinus rhythm
Cervical and cerebral vessels investigation	Nonsignificant stenosis of carotid artery	Nonsignificant stenosis of carotid artery	Normal	Not done	Nonsignificant stenosis of carotid artery	Nonsignificant stenosis of carotid artery	Aneurysm
COVID-19 symptoms	Chills, vomiting	Dyspnea, nausea, vomiting, diarrhea	Dyspnea	Presentation symptoms as CVST and dyspnea	Fever	Presentation symptom	Presentation symptom

*Score on the NIHSS range from 0 to 42, with a higher number indicating more severe stroke, *Score on the MRS range from 0 to 6, with a higher number indicating more severe stroke. NIHSS=National Institutes of Health Stroke Scale; MRS=Modified Rankin Scale; CT=Computed tomography; MRI=Magnetic resonance imaging; MRV=Magnetic resonance venography; CTA=Computed tomography angiography; TR=Tricuspid regurgitation; MR=Mitral regurgitation; ECG=Electrocardiogram; CVST=Cerebral venous sinus thrombosis; COVID-19=Coronavirus disease 2019

of AIS in COVID-19 patients.^[2-5,12] Indeed, we included stroke with specific symptom (clinically stroke syndrome), therefore, maybe some stroke patients with nonspecific stroke symptom were overlooked.

Similar to report from other studies,^[1-5,12,13] these patients were associated with severe disease and had a higher incidence of risk factors such as hypertension, diabetes, coronary artery

disease, and previous cerebrovascular disease. Average time of onset of stroke after COVID 19 diagnosis was lower than Chinese studies.^[1] Avula *et al* study^[13] showed stroke can be as a presenting symptom of COVID 19, we showed stroke as a presenting symptom of COVID-19 in near to 50% of patients.

Although Avula *et al.*^[13] revealed that the most plausible mechanism of early cerebrovascular accidents in COVID-19

could be hypercoagulability leading to macro and micro *in situ* thrombi formation in the vessels, we showed that CE was the most subtype of AIS (60%) and the rest was ESUS (40%). Similar to our study, other recent studies^[2,3,12] showed ESUS and cryptogenic stroke was near to 50% of AIS in COVID-19 patients. Some studies showed that COVID-19 patients are likely to be at risk of arrhythmia due to underlying comorbidities (myocardial injury, myocardial ischemia, hypoxia, shock, and electrolyte disturbances), polypharmacy, and the disease process.^[14,15] All of these mechanisms could be risk factors of CE in COVID-19 patients. As we showed, one patient with new atrial fibrillation, one patient with stress cardiomyopathy (low-ejection fraction), and one patient with myocardial infarction developed embolic stroke.

CONCLUSION

Stroke was an uncommon manifestation in COVID-19 patients. CE was a common subtype of stroke in COVID-19 patients in our center, and it can be due to arrhythmia because of underlying comorbidities, polypharmacy, and disease process.

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Conflicts of interest

There are no conflicts of interest.

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