COVID-19 Respiratory Illness and Subsequent Cerebrovascular Events, the Initial Iranian Experience

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Objectives: COVID-19 disproportionately affects older adults and individuals with cardiovascular co-morbidities. This report presents fifteen patients who had COVID-19 respiratory illness followed by cerebrovascular events. Materials and Methods: A call by the Iranian Neurological Association gathered cases across the country who developed neurological symptoms attributed to hemorrhagic or ischemic stroke after a definite or probable Covid-19 respiratory illness. Definite cases were those with a typical respiratory illness, positive nasopharyngeal Covid-19 PCR test, and chest CT consistent with Covid-19 infection. Probable cases were defined by a typical respiratory illness, history of contacts with a Covid-19 case, and chest CT characteristic for Covid-19 infection. Results: Fifteen patients (12 men and 3 women) with an age range of 38 to 93 years old (median: 65 years old) were included. Fourteen patients had a first-ever acute ischemic stroke and one patient had a subarachnoid hemorrhage. Eleven patients (73%) had previous cardiovascular comorbidities. The median time between respiratory symptoms and neurological symptoms was seven days (range 1-16 days). Stroke severity in two patients was mild (NIHSS ≤ 6), in six patients moderate (NIHSS: 7-12), and in seven patients severe (NIHSS ≥13). One patient received intravenous tissue plasminogen activator (IV-tPA) with improved neurological symptoms. Six out of 15 patients (40%) died.
Introduction

Coronavirus disease 2019 (COVID-19) infection has rapidly spread across the world, currently affecting more than 39 million people, leading to major societal, economical and health care system disruptions. Older adults and those with vascular co-morbidities are disproportionately affected. More than one third of patients who required intensive care unit admission had at least one underlying vascular risk factor. In addition to respiratory symptoms, COVID-19 infection can also lead to hematological and cardiac complications. ACE2 (angiotensin-converting enzyme 2) receptor, a key cell surface protein facilitating SARS-CoV-2 (the virus that causes COVID-19) entry to the cells, is found in various cells including vascular endothelium and neurons. Therefore, rising concerns about potential neurovascular complications of COVID-19 infection have biological plausibility. In this report, we present clinical data on fifteen Iranian patients who initially presented with respiratory symptoms typical for COVID-19, but subsequently developed neurological symptoms with evidence of ischemic stroke or subarachnoid hemorrhage (SAH) on imaging.

Methods

This is a case series of patients with stroke and a previous diagnosis of COVID-19 with respiratory illness from February 19, 2020 (the date first COVID-19 infection documented in Iran) to March 19, 2020. A survey was sent to all members of the Iranian Neurological Association, which is a non-profit/non-governmental organization with approximately 1400 adult neurologists as members. Neurologists were asked to report patients who developed acute cerebrovascular events after a documented COVID-19 respiratory infection. Cases were those with initial typical respiratory illness (cough and shortness of breath) associated with systemic symptoms including fever, chills or myalgia with positive COVID-19 PCR test and with characteristic findings on chest computed tomography (CT). Cases without PCR testing were defined by the same typical systemic and respiratory manifestations, reported contact with known COVID-19 patients and with characteristic chest CT findings which has 97% sensitivity in COVID-19 patients. Data on the total number of COVID-19 cases in Iran during the study period was obtained using World Health Organization situation report (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports).

Eligible cases needed to have acute neurological symptoms following the respiratory illness. Further demographic and acute illness related data including date of initial symptoms, type of symptoms, history of close contacts with other patients with COVID-19, interval between manifestations of COVID-19 and neurological symptoms (days) were obtained for all eligible patients. Previously established clinical guidelines were applied for the diagnosis of ischemic and hemorrhagic stroke and subarachnoid hemorrhage. Severity of the COVID-19 was measured by Ordinal Scale for Clinical Improvement which has been proposed by a special World Health Organization (WHO) committee. This is a clinical scale which includes uninfected (0 score), ambulatory (1 and 2 scores), hospitalized mild disease (3 and 4 scores), hospitalized severe disease (5-7 scores), and death (8 score) (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf).

Treatind neurologists provided data on vascular risk factors and comorbidities including hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation and other arrhythmias, congestive heart failure, valvular heart disease and ischemic heart disease. All patients had noninvasive cardiac investigations including electrocardiography (ECG) and transthoracic echocardiography (TTE). Due to COVID-19 outbreak and resource re-allocation across Iranian healthcare centers, transcranial Doppler (TCD), CT angiography (CTA) and/or magnetic resonance angiography (MRA) were not performed in reported cases. Patients with prior stroke, vasculitis, arterial dissection, fibromuscular dysplasia, Moyamoya disease or any other established cerebrovascular diseases were not included. Modified Rankin scale (mRS) of patients in the last phone follow-up after stroke was recorded. National Institutes of Health Stroke Scale (NIHSS) at the time of stroke diagnosis was documented for all patients and categorized into mild (≤ 6), moderate (7-12) and severe stroke (≥13). This study was approved by the institutional review board (IRB) of Shiraz University of Medical Sciences. Informed consent was obtained from the patient and/or first-degree relatives.
Results

Over the inclusion time period, 15 patients out of 18407 COVID-19 cases (0.81 per 1000 cases, 95% confidence interval 1.3-0.49) were reported to have cerebrovascular events. We included 12 men and three women (median age: 65 years). They ranged from 38 to 93 years-old (median: 65 years-old) and came from all geographical regions in Iran (eight centers). Thirteen patients were from urban areas and two patients were from rural areas. Table 1 summarizes the demographic and clinical characteristics of these patients. Systemic manifestations of COVID-19 infection include fever, cough, dyspnea and myalgia. All patients were hospitalized due to COVID-19 respiratory symptoms. Interval time between systemic manifestations and neurological symptoms ranged from one to 16 days (median: 7 days). Median of severity of the COVID-19 in in ordinal scale for clinical improvement was 6. Fourteen patients had acute ischemic stroke and one patient had subarachnoid hemorrhage (Fig. 1). Among patients with ischemic stroke, two patients had bilateral multifocal stroke, nine had unilateral, two had striatocapsular, one had subcortical lacunar and two had brainstem strokes. Eleven patients (73%) had underlying cardiovascular risk factors. All the patients underwent TTE. None of the patients had myocarditis, endocarditis or pericarditis. Spot ECGs and in-hospital cardiac monitoring did not show evidence of atrial fibrillation or other arrhythmias for any patient. Similarly, none of our patients had deep vein thrombosis or severe hemodynamic instability at the time of stroke diagnosis. One patient (case number 10) was diagnosed with disseminated intravascular coagulation (DIC). Lymphopenia (absolute lymphocyte counts less than 1500 mm³) was seen in 12 patients (80%) at the time of stroke diagnosis. A significant pro-inflammatory state assessed by C-reactive protein (CRP) was seen in all patients who were tested (13 patients). 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Table 1. Characteristics of 15 COVID-19 patients with subsequent acute cerebrovascular events.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
<th>Patient 9</th>
<th>Patient 10</th>
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<td>65</td>
<td>83</td>
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<td>Severity of covid-19 according to OSCI</td>
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<td>8</td>
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<td>Time from covid-19 symptoms to stroke symptoms, days</td>
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<td>7</td>
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<tr>
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<td>CT</td>
<td>CT</td>
<td>MRI</td>
<td>CT</td>
<td>CT</td>
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<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>MRI</td>
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<tr>
<td>Initial severity of stroke (NIHSS)</td>
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<td>Severe</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild ≤ 6</td>
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<td>6</td>
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<td>3</td>
<td>4</td>
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<td>6</td>
<td>3</td>
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Abbreviations: NA: not available, mRS: modified ranking scale, PCR: polymerase chain reaction, NIHSS: National Institute of Health stroke scale, OSCI: ordinal scale for clinical improvement, OSCI: ordinal scale for clinical improvement.
Also, cardiac evaluation was limited to TTE and more sophisticated testing such as transesophageal echocardiography, cardiac MRI and long-term ECG monitoring could not be performed. In addition, the lack of detailed cerebrovascular imaging including brain and neck CTA and MRA and autopsy data was a major barrier in determining the etiology and mechanisms of stroke in our patients.

The data in this report were gathered early during the COVID-19 pandemic in the midst of outbreak in Iran which lead to major disruptions in traditional stroke care, which may have adversely impacted patient outcomes. However, the potentially worse outcomes in this setting may also represent the clinical environment in many other countries during this pandemic. It should be noted that in this study there was no control group to compare characteristics and outcomes in stroke patients with and without COVID-19 and we suggest future studies involving all patients with stroke during the pandemic.

Increasing number of patients in the world are being affected by this acute respiratory condition requiring intubation and sedation which can mask neurological symptoms and early recognition of stroke. Stroke can lead to worse clinical outcomes and long-term disabilities in these patients. In this group of patients, we observed that baseline cardiovascular co-morbidities in combination with significant inflammatory was a prominent feature and was associated with higher risk of mortality and disability. This report can potentially stimulate further research on the mechanistic underpinnings linking SARS-CoV2 infection and cerebrovascular outcomes, particularly in high-risk patient populations. Further prospective and larger studies with more complex methodologies and through ancillary investigations are critical and necessary to improving stroke care during and after this pandemic.

Declaration of Competing Interest

Nothing to report.
Author contributions
A.B., B.S.; conception and design of the study, acquisition and analysis of data, drafting the manuscript and figures. M. M., F.A., S.K., L.P., Z.B., S.A.B., Z.H., E.M, H.M, S.P., N.R., A. S., M.S., M.R.N.; acquisition and analysis of data, revision the manuscript and figure. R.B.S., A.B., F.S.; conception of the study, revision of the manuscript and figures.

Acknowledgment
This work used no available grant and individuals contributed using their own time and budget.

References