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CASE SERIES

Acute Ischemic Stroke as Presenting Symptoms in COVID-19 Patients- Case Series

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ABSTRACT

The Coronavirus disease-2019 (COVID-19) pandemic which started in December 2019 affected almost the entire globe. India is witnessing the second wave of pandemic from mid-February 2021 wherein cases of COVID-19 are rising sharply. Apart from constitutional symptoms, other common symptoms involve respiratory and gastrointestinal systems. Here, we present case series of three COVID-19 positive patients, who primarily reported to hospital with neurological symptoms of acute stroke. Polymerase chain reaction confirmation of COVID-19 infections was done. All of them had radiological evidence of acute ischemic stroke and lung involvement due to COVID-19 infection. We have also illustrated the clinical manifestation, radiological findings, and the clinical course of all these patients. COVID-19 is a pro-inflammatory, hypercoagulable state, with increased risk of arterial and venous thrombosis. This leads to acute ischemic cerebrovascular accident. In small set of patients though symptomatic for COVID-19, neurological symptoms could be the presenting symptom for seeking medical aid. It is, therefore, suggested to observe any neurological symptoms suggestive of stroke in the early days of COVID-19 infection.

Key words: Coronavirus disease-2019 infection, Hypercoagulable state, Ischemic stroke

INTRODUCTION

In December 2019, the world witnessed the emergence of a new disease, Coronavirus Disease-2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case was reported from Wuhan, Hubei Province, China. The disease showed rapid progression with the WHO declaring it as a pandemic on March 11, 2020.[1] India is witnessing the second wave of pandemic from mid-February 2021 wherein cases of COVID-19 are rising sharply. Main symptoms include fever, cough, sore throat, breathlessness, myalgia, loss of taste, loss of smell, and diarrhea. The clinical manifestations of COVID-19 range from completely asymptomatic infection to severe pneumonia, myocarditis, acute respiratory distress syndrome, acute kidney injury, multi-organ dysfunction, to death. It is also proposed that it leads to multiple neurological manifestations, involving both the central nervous system and peripheral nervous systems such as headache, vertigo, ataxia, cognitive impairment, Guillain-Barre Syndrome, and cerebrovascular accidents.[2] The COVID-19 infection is a pro-inflammatory and hypercoagulable state with an increased risk of arterial and venous thrombosis. Changes due to COVID-19 infection causes inflammation and hypoxia subsequently leading to ischemia and acute ischemic stroke.[3] Nevertheless, the severity of lung involvement and occurrence of acute stroke is not yet established. This article aims to present the COVID-19 cases that reported primarily with an acute

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stroke instead of main symptoms of COVID-19 with varied spectrum of lung involvement.

CASE REPORT

We present three patients, who primarily reported to the hospital with acute neurological symptoms suggestive of acute cerebrovascular accidents. They had symptoms of COVID-19 though not serious enough to seek medical aid but were found positive by polymerase chain reaction (PCR) for COVID-19 infection. They gave no history suggestive of any cardiac disease/arrhythmia, previous stroke, primary hypertension, or dyslipidemia. Tables 1 and 2 describes the demographic profile, clinical features, and baseline laboratory investigations.

Table 1: Patient's profile

Bio-social Profile	Patient 1	Patient 2	Patient 3
Demographic Profile			
Age (years)	52 years	49 years	66 years
Sex	Female	Male	Female
Risk factors for stroke			
Hypertension	Nil	Nil	Yes
Diabetes mellitus	Yes	Nil	Nil
Hyperlipidemia	Nil	Nil	Nil
DVT/PTE	Nil	Nil	Nil
Previous stroke	Nil	Nil	Nil
Atrial fibrillation / flutter	Nil	Nil	Nil
Symptoms			
COVID-19 symptoms	Fever, Cough, Myalgia	Fever, Cough, Breathlessness, Myalgia, Headache	Fever
Stroke symptoms	Weakness left upper and lower limb, facial asymmetry	Altered sensorium, facial asymmetry	Weakness right side, altered sensorium
NIHSS	13	15	22
Findings			
SPO2% (room air) (On admission)	93%	89%	86%
O2 Supplementations	Nasal prong/ HFNO/ Mechanical Ventilator	HFNO	Nasal prong/ HFNO/ Mechanical Ventilator
Duration between onset of symptoms for COVID-19 and stroke	2 days	4 days	4 days
Duration of stay in the hospital	17	7	20
Final disposal	Expired	Discharged	Expired

COVID-19: Coronavirus disease 2019, HFNO: High-flow nasal oxygen

Case 1

A 52-year-old female with a history of type II diabetes mellitus was was brought to the emergency room with history of sudden onset weakness over the left side of the body and inability to speak since 6 hours. There was a preceding history of fever, cough, and malaise of 2 days duration. On examination, she was febrile (Temperature - 101°F) with tachycardia (heart rate [HR] -110/min), tachypnea (respiratory rate [RR] 26/min), and reduced oxygen saturation (SpO2 - 93%). Chest evaluation revealed basal crackles in the bilateral infra scapular region. On neurological examination, she had Glasgow Coma Scale of 15/15, left VII nerve Upper Motor Neuron palsy, power on the left side - 3/5, and extensor plantar reflex. Findings of computed tomography (CT) of the brain and chest are shown in Table 3 (1a and b). Electrocardiogram was within the normal limit. The blood evaluation revealed polymorpho leukocytosis. The PCR for COVID-19 was positive. She was started with remdisevir, broad-spectrum antibiotics, low-molecular-weight heparin (LMWH), steroids, and other supportive measures. Initially, she was put on high-flow nasal oxygen (HFNO). However, as the respiratory distress worsened, she was placed on a mechanical ventilator. Eventually, she developed sepsis with multiorgan dysfunction and finally succumbed to her illness.

Case 2

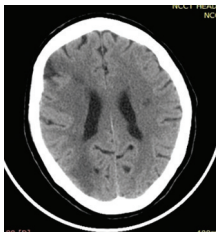
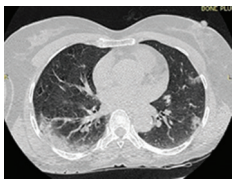
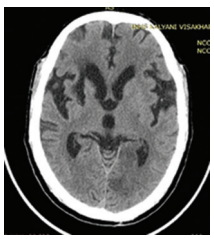
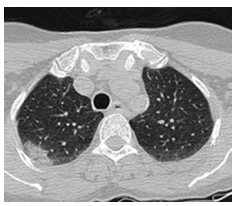
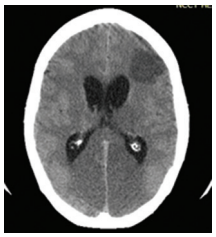
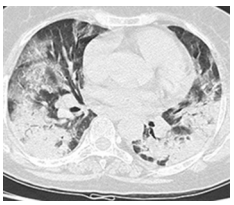
A 49-year-old male with no previous comorbidity presented with complaints of altered sensorium for 1 day. He had a history of fever, cough, breathlessness, and myalgia of 4 days duration. On examination, temperature was 102°F with HR- 122/min, BP- 180/102 mm Hg, and SpO2-90%. He was drowsy with NIHSS score of 15/42. Chest evaluation

Table 2: Summary of laboratory investigations

Laboratory Investigations	Patient 1	Patient 2	Patient 3
Hb (g/dl)	11.8	11.3	12.2
TLC (cells/mm^3)	16500	14,000	13,900
DLC (P/L/E/M)	76/19/1/6	82/10/5/3	90/05/01/04
Platelet (cells/mm^3)	291000	2,11,000	2,56,000
Urea (mg/dl)	41	32	44
Creatinine (mg/dl)	1.3	1.2	1.4
Na (mEq/L)	140	136	138
K (mEq/L)	3.9	4.4	4.2
SrBil (mg/dl)	0.8	1.0	0.4
AST (IU/L)	20	36	48
ALT (IU/L)	30	44	84
CRP (mg/L)	44.6	32.0	56.4
Ferritin (ng/ml)	1210	722	1667
D-Dimer (mcg/ml)	4.2	1.1	3.6
INR	1.0	1.0	1.15

Hb: Hemoglobin, TLC: Total leukocyte count, DLC: Differential leukocyte count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein

Table 3: Images and findings of NCCT Brain and HRCT Chest

S. No.	Images	Findings
Patient 1	 1a–Brain	Area of hypodensity (mean HU-18.5) involving right middle cerebral artery (MCA) territory involving gray and white matter areas of right frontal, parietal, temporal lobes including centrum semiovale, corona radiate, basal ganglia, internal capsule, and right peri-ventricular trigone area. Suggestive (s/o) of acute infarct right MCA territory
	 1b-Chest	Multifocal ground-glass opacities in bilateral lungs with patchy consolidation in the bilateral lower lobe. Suggestive of viral pneumonia with a high suspicion of COVID-19 (CO RADS-5)
Patient 2	 2a-Brain	Areas of hypodensity (mean HU-20) aseen involving the medial aspect of the left occipital lobe and splenium of the corpus callosum on the left side. S/o acute infarct left PCA territory
	 2b-Chest	Multifocal ground-glass opacities in bilateral lungs with patchy consolidation right lower lobe S/o viral pneumonia with high suspicion of COVID-19 (CO-RADS-5)
Patient 3	 3a-Brain	Multiple wedge shaped areas of hypodensities (mean HU- 20) involving cortex as well as underlying white matter are seen in bilateral frontal and parietal lobes (left>right), bilateral occipital lobes, posterior aspect of the left temporal lobe, and left thalamus. Superior aspects of bilateral cerebellar hemispheres and middle cerebellar peduncles, the midbrain, and pons appear swollen and show hypodensity (mean HU-20), Suggestive of bilateral acute infarcts involving both anterior and posterior circulation
	 3b-Chest	Presence of multifocal ground-glass opacities in bilateral lungs, suggestive of viral pneumonia with a high suspicion of COVID-19 (CO-RADS-5)

NCCT: Noncontrast computed tomography, HRCT: High-resolution computed tomography, PCA: Posterior cerebral artery

revealed the presence of bilateral basal crackles. PCR for COVID-19 was positive with raised C-reactive protein (CRP) and serum ferritin. Findings of CT brain and chest are shown in Table 3 (2a and b). The patient was started on remdesivir, broad-spectrum antibiotics, steroids, LMWH, and HFNO. With a favorable response, the patient was discharged after 7 days.

Case 3

A 65-year-old female with no known comorbidity reported with acute onset right-sided weakness associated with altered sensorium for 12 h. There was a history of fever, cough, and breathlessness for 4 days. There was no history of seizure or trauma. On examination, the temperature was 100.4°F with HR-118/min, RR-28/min, and SpO2- 86%. Chest examination revealed the presence of bilateral crackles (left>right). She had raised CRP and serum ferritin and polymorpho-leukocytosis with a shift to left. PCR for COVID-19 was positive. Arterial blood gas revealed partially compensated mixed acidosis with a lactate level of 4.3. Findings of CT brain and chest are shown in Table 3 (3a and b). The patient was started with remdesivir, broad-spectrum antibiotics, steroids, LMWH, and other supportive medicines. Initially, she was kept on HFNO. Eventually, she was intubated and placed on a mechanical ventilator due to respiratory distress. She did not respond favorably to the treatment and succumbed to her illness after 20 days.

DISCUSSION

Respiratory tract and gastrointestinal symptoms are the most common symptoms of COVID-19. Among neurological symptoms; anosmia, hypomania, and headache are prominent. Severe but uncommon neurological symptoms include acute ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis.[3]

In our case series, patients had few symptoms of COVID-19 and mainly reported neurological symptoms relating to acute stroke. They had reduced oxygen saturation and pulmonary

involvement, requiring oxygen support. One patient was detected with multiple ischemic infarcts involving both posterior cerebral artery and middle cerebral artery territories. Two patients, who had severe pneumonia, finally succumbed due to respiratory failure, sepsis, and multiorgan dysfunction. Acute ischemic stroke in patients with COVID-19 infection may be due to known causes of stroke such as atherosclerosis, hypertension, and atrial fibrillation. Ischemic stroke has been recognized as a complication of COVID-19. The exact mechanism for the cerebrovascular events in COVID-19 is not fully known. With the present understanding, the mechanism for acute ischemic stroke includes hypercoagulable state, vascular endothelial injury (vasculitis), and cardiomyopathy induced by COVID-19 infection.[2-4]

Angiotensin-converting enzyme-2 (ACE-2) has an important role in COVID-19 infection. SARS-CoV-2 binds to ACE-2, an essential counter-regulatory enzyme that converts angiotensin I to angiotensin II.[5] ACE-2 is present in nearly all human tissues, ranging from endothelial cells of small and large arteries and veins, type I and type II alveolar epithelial cells in lungs, nasal and oral mucosa, and the nasopharynx.[6] SARS-CoV-2 binds with ACE-2, causing inhibition and downregulation of ACE-2. This leads to an increased level of Angiotensin I, causing a pro-inflammatory state in the body, vasoconstriction, sodium retention, and fibrosis all over the body. This proinflammatory state is evident by higher plasma levels of cytokines, granulocyte colony-stimulating factor, IgG-induced protein 10, monocyte chemo-attractant protein-1, macrophage inflammatory protein 1-alpha, and tumor necrosis factor α resulting in a hypercoagulable milieu.[7] This hypercoagulable state possibly increases the incidence of thrombotic events in COVID-19 patients. An autopsy study of the lungs in the patients with COVID-19 infection revealed microvascular platelet-rich depositions in the small vessels of the lungs suggestive of thrombotic microangiopathy.[8]

One of the studies reported the median duration of occurrence of cerebrovascular accident from first symptoms of COVID-19 infection as 10 days, whereas the other reported 8–24 days.[9,10] In our study, we found the occurrence of acute ischemic stroke as early as 2–4 days after the onset of COVID-19 related symptoms. This suggests that small subset of COVID-19 patient may develop acute ischemic stroke in early stage of disease. However, more multicentre studies may needed to know the occurrence of similar event in cases of COVID-19 infections.

CONCLUSION

COVID-19 may lead to acute thrombo-embolic events such as an acute ischemic cerebrovascular accident. In this case series, we reported COVID-19 patients with neurological symptoms suggestive of stroke in the early days of COVID-19 infection, without significant symptoms of COVID-19 infection. Hence, to conclude, neurological symptoms should be assessed in the early stages of infection of COVID-19 infections for better management.

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