Association of COVID-19 Infection and Juvenile Stroke: a Case Series

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Abstract

Ischemic stroke has been increasingly reported as a consequence of COVID-19 infection. However, the underlying etiology is not well determined. The objective of this study is to discuss association of juvenile stroke with COVID-19 infection. We analyzed 5 COVID-19 positive and stroke patients with a mean age of 41.2 years-old. Three patients developed large vessel occlusion, one small vessel occlusion and one PRES with superimposed lobar ICH, respectively. The mean initial NIHSS of our patients was 11.6. Except the one with massive cerebellar infarct, a desirable outcome occurred with a mean mRS 2.6 at discharge. The mean ESR and CRP level was elevated to 30.4 ml and 32 mg/dl. The severity of COVID-19 infection was considered mainly as mild. COVID-19 infection has the potential to induce hypercoagulability state contributing to stroke development even in the mild form of disease.

Keywords: Cerebrovascular Accident, CVA, Stroke, COVID-19, Novel Coronavirus

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BACKGROUND

The novel coronavirus disease (COVID-19) first emerged in China with a cluster of unexplained pneumonia which soon has turned into a global pandemic [1,2]. There are increasingly reports of acute cerebrovascular accidents (CVA) associated with COVID-19 infection in the literature. However, the exact underlying pathophysiology is undetermined [3–5]. It is postulated that SARC-CoV 2 acts via the ACE2 (angiotensin converting enzyme II) receptor, which is heavily expressed in myocardium, vascular endothelium, and arterial smooth muscle leading to thrombogenesis. The prothrombotic state associated with increased D-dimer levels in the course of COVID-19 infection might also predispose to thrombotic events [5–7]. Interestingly, cases of juvenile stroke associated with COVID-19 have been reported despite the presence of contributing risk factors as advanced age, hypertension

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and cardiovascular risk factor [8].

Given the increasing prevalence of COVID-19 infection and its cerebrovascular complications on the one hand and the significant impact of stroke on the other, it is crucial to understand the exact relationship between COVID-19 and stroke. Herein, we aimed to report five cases of juvenile stroke associated with COVID-19 infection to provide a comprehensive review of the cerebrovascular complications of COVID-19 in the youth.

CASE PRESENTATION

Case 1

A 43 year-old male presented to the emergency department (ED) with a two-day history of progressive ataxia. He also mentioned intermittent cough and exertional dyspnea over the last three days. The habitual history was remarkable for opium addiction and heavy smoking. On examination, the vital signs were normal. Pulmonary auscultation indicated bilateral fine crackle in the lungs. The neurological examination was notable for wide based gait with tendency to fall to the right along with incoordination of right side. The National Institute of Health Stroke Scale (NIHSS) was 6.

Investigations

The brain computed tomography (CT) scan demonstrated acute infarct in right cerebellar hemisphere with mild hydrocephalus. The chest CT showed diffuse ground-glass opacities. Blood work was significant for leukocytosis (WBC 10000/μl with 12% lymphocyte). Erythrocyte sedimentation rate (ESR) was elevated to 40 ml and C-reactive protein to 45 mg/dl. COVID-19 polymerase chain reaction (PCR) detected the virus.

Treatment, outcome and follow-up

The patient was admitted to the intensive care unit (ICU) and treated with unfractionated heparin with continuous infusion of 1000 units/hr, aspirin 80 mg, and osmotherapy with mannitol 20% at a dose of 75 ml every 6 hours. Additionally, hydroxychloroquine and ceftriaxone was instituted. The echocardiogram (ECG) was normal and the telemetry monitoring did not reveal abnormal heart rhythm. On hospital day 2, the patient developed fever, severe respiratory distress and loss of consciousness leading to intubation. A repeat brain CT demonstrated progression of hydrocephalus and generalized edema. The chest CT demonstrated evidence of acute respiratory distress syndrome (ARDS). The patient was deemed not a candidate for neuro-intervention due to poor functional status. He eventually deceased a day after intubation.

Case 2

A 41 year-old female with a week history of fever, cough, and dyspnea presented to the ED with right hemiparesis and dysarthria since an hour before arrival. Her past medical history remarkable for gestational diabetes mellitus. Initial vital signs were revealed temperature of 38.0°C, RR of 22, HR of 100, blood pressure of 125/75, saturating 95%. The neurological examination was notable for right facial droop, broca aphasia and right hemiparesis. The NIHSS was 16.

Investigations

Blood work was considerable for leukocytosis (WBC 12800/ μl with 6% lymph) with elevated ESR to 11 ml and C-reactive protein to 36 mg/dl. The initial brain CT was unremarkable and the chest CT was suggestive of COVID-19.

Treatment, outcome and follow-up

The patient received 6 mg IV bolus rtPA over 1 minute followed by 52 mg IV infusion over 60 minutes. As COVID-19 was suspected, hydroxychloroquine, ceftriaxone and azithromycin was instituted. The diagnosis of COVID-19 was later confirmed by COVID-19 PCR. The reevaluation of the patient over 24 hours demonstrated a NIHSS of 10. The repeated brain CT yielded acute fragmented infarction in superior middle cerebral artery (MCA). The patient was then treated with aspirin 80 mg daily. Brain and cervical CT angiography, trans-thoracic and esophageal echocardiography, coagulation and vasculitis tests were unremarkable. The patient was discharged ten days later with a NIHSS 5 and Modified Rankin Scale (mRS) 2.

Case 3

A 46 year-old female with a past medical history of mitral valve stenosis, transient ischemic attack (TIA) and thyroidectomy presented to the ED with left hemiplegia

since 75 minutes before arrival. Her medications included levothyroxine, aspirin and propranolol. On examination, her vital signs were within normal except for low μl saturation (87% on room air and 92% by nasal oxygenation). The neurological examination was significant for gaze to the right, slurred speech and left hemiparesis. The NIHSS was 18.

Investigations, treatment, outcome and follow-up

The laboratory examination revealed WBC 19200/μl with 5% lymph. The brain CT was negative for any acute changes. Subsequently, reperfusion therapy by 6 mg IV bolus rtPA over 1 minute followed by 57 mg IV infusion over 60 minutes was started. Five hours later, the patient suddenly developed acute respiratory distress. The patient got intubated and underwent chest CT regarding the respiratory distress in the absence of angioedema symptoms which revealed diffuse ground-glass opacities in both longs. Treatment with meropenem, vancomycin and Kaletra was started. Two hours later, the patient experienced two episodes of generalized tonic-clonic seizure which was fully controlled by Na-valproate .The repeated brain CT was unrevealing. Over 24 hours, the patient improved dramatically. She was separated from the ventilator. The next brain CT revealed fragmented acute infarction in stem of right MCA without hemorrhagic transformation. The patient then started on aspirin 80 mg daily and the antibiotic therapy continued. The brain and cervical CT angiography was unremarkable. The trans-esophageal echocardiogram revealed ejection fraction 50% , basal septal hypertrophy of 10 mm, severe left atrium enlargement , progressive rheumatism stenosis mitral stenosis , moderate mitral regurgitation and moderate aortic insufficiency. The patient was candidate for anticoagulant therapy and mitral valve replacement. The nasopharyngeal PCR and serum IgM was positive for COVID-19. The patient improved over hospitalization and eventually was discharged with a complete recovery (NIHSS 5 and mRS 1).

Case 4

The patient was a healthy opium addict male aged 39 years who was admitted with a diagnosis of COVID-19. His laboratory findings were significant for leukocytosis (WBC 19700/μl with 5% lymph). However, ESR and CRP level were within normal. On day three, the patient suddenly developed three episodes of generalized tonic-clonic seizure in conjunction with hypertension crisis. On neurological examination, the patient was confused and left hemiplegia was evident.

Investigations

The brain CT revealed bilateral cortical and subcortical parieto-occipital hypo-attenuation as well as a cortical hemorrhage in the right parietal lobe. Brain magnetic resonance imaging (MRI) was compatible with posterior reversible leukoencephalopathy syndrome (PRES) and superimposed acute hemorrhage in the right parietal lobe. The brain MR venography and angiography, echocardiogram, and telemetry monitoring were unrevealing.

Treatment, outcome and follow-up

The medical treatment with labetalol infusion at a dose of 1 mg/min and antiepileptic were initiated leading to significant clinical improvement over a week. The patient was discharged with a NIHSS 8 and mRS 3.

Case 5

The patient was a severe obese 37-year-old man who presented to the ER with acute left hemiparesis upon awakening. The neurological examination was notable for left hemiparesis with an MRC scale of 4/5. The initial NIHSS was 4.

Investigations

The brain CT was unremarkable. The chest CT revealed bilateral ground-glass opacities in less than 50% of the lungs. The laboratory examination was notable for leukocytosis (WBC 11200/μl with 25% lymph) and elevated ESR to 56 ml and C-reactive protein to 18 mg/dl. The brain MRI revealed an acute lacunar infraction in right putamen. The extensive etiological study by brain and cervical CTA, trans-thoracic and esophageal echocardiogram were normal. Furthermore, PCR assay for COVID-19 was positive.

Treatment, outcome and follow-up

The patient was treated with aspirin, Plavix, hydroxychloroquine and ceftriaxone. He was discharged

from the hospital with a NIHSS 3 and mRS 1 after a week. The summary of patients' characteristic are described in Table 1.

DICUSSION

We report five cases of acute stroke in association with COVID-19 infection in patients younger than 50 years of age. Although there is no exclusive age definition of "juvenile" stroke, the majority of the studies considered 50 or 55 years as the cut-off [9]. The mean age of our patients was 41.2 years old. Only one patient had a cardiovascular risk factor which led to cardio-embolic type of stroke. Three patients had mild COVID-19. The ESR level was

Table 1: Clinical Characteristics of Five Young Patients Presenting with acute cerebrovascular accidents in association with COVID-19

patients / variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
age	43	41	46	39	37
sex	Male	Female	Female	Male	Male
Medical history and risk factors	Opium addiction and smoker	Gestational Diabetes mellitus	Mitral stenosis, TIA, hypothyroidism, (total thyroidectomy)	Opium addiction and smoker	Severe obesity
Medications	None	none	Levothyroxine ,ASA ,propranolol	None	None
Initial NIHSS	6	16	18	12	6
NIHSS score At 24 hr	30	10	5	12	6
NIHSS score At last follow-up	-	5	0	5	3
MRS at discharge	6	2	1	3	`1
Time to presentation- hr	48 hr	1hr	75 min	The patient developed acute focal neurological deficit over hospitalization	Upon awakening (unknown time)
Signs and symptoms of stroke	ataxia	Right hemiparesis, broca aphasia	Left hemiparesis, slurred speech, Gaze to the right side	Left hemiplegia and three episodes of seizure	Left hemiparesis
Vascular territory	Right cerebellar ischemia	Left superior MCA	Right stem of MCA (fragmented)	PRES and right lobar ICH	Penetrating branches of right MCA
Imaging for diagnosis	CT scan	CT scan	CT scan	CT scan, MRI	CT scan, MRI
CT or MRA	Normal	Normal	Normal	Normal	Normal
Echocardiogram	Normal	Normal	Normal	EF 50% , basal septal hypertrophy of 10 mm, severe left atrium enlargement, progressive rheumatism mitral stenosis ,moderate MR, moderate AI	Normal

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patients / variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Treatment for stroke	Anticoagulant , ASA	RTPA followed by ASA	RTPA followed by ASA	Anti-hypertensive (labetalol, captopril)	ASA, Plavix
Covid-19 symptoms	Intermittent cough , exertional dyspnea	Fever, dyspnea, cough	O_2 saturation decline	Cough, Fever	Asymptomatic
White-cell count- per mm^3	10000	12800	19200	19700	11200
Lymph %	12%	6%	5%	5%	25%
Platelet count— per mm3	283	107	315	150	221
Prothrombin time — sec	13.4	19.5	14	12.8	13.2
Activated partial-thromboplastin time— sec	26.5	26	26	25	25
ESR	40	11	42	3	56

elevated in four patients with a mean of 30.4 ml. Average time of onset of stroke after COVID-19 diagnosis was four days. On admission, the mean NIHSS score was 11.6. The mean mRS score at discharge was 3.25. Although one patient died, a considerable improvement was evident among others with a mean NIHSS 3.25 at discharge. The administered therapy was rtPA followed by aspirin for two patients, anticoagulant for one and double antiplatelet for one. Symptom therapy was adopted for the one with PRES. Three patients developed large vessel occlusion in both anterior and posterior circulation.

While there is limited data on the association of COVID-19 and ischemic stroke, the prevalence of ischemic stroke in COVID-19 patients is estimated at 1.6% in a meta-analysis [10]. However, the data from China demonstrated higher incidence (approximately 5%) [11,12]. As the juvenile stroke has a greater social impact than those of stroke in elder population, more attention has taken toward it in association with COVID-19 as the study of Thomas J. Oxley et al. who reported a case series of large-vessel stroke associated with COVID-19 in the young patients [8,9].

COVID-19 infection is associated with a prothrombotic state leading to venous and arterial thromboembolism. It might also induce pro-inflammatory cytokine storm leading to cellular activation with expression of tissue factor, coagulation activation and thrombin generation. Other contributing factors to develop stroke are cardio embolism from virus-related cardiac injury occurring in 20–30% of hospitalized patients and direct viral invasion of the nervous system [5–7,11–14].

It should be noted that, of the 61 patients hospitalized with acute stroke during the first four months of the pandemic in our center, five patients (8.2%) were classified as juvenile stroke all of whom were associated with COVID-19. Additionally, except the one with an underlying cardio-embolic disease, no clear source of stroke was identified in others meeting the criteria for cryptogenic stroke which was significantly higher than the overall prevalence of cryptogenic stroke highlighting the hypothesis of a hypercoagulable state or pro-inflammatory reactions following COVID-19. However, due to the financial issues and insufficient insight in the early stage of the disease, we did not perform ancillary examination

as assessing the level of interleukins.

Despite the initial impression linking stroke to severe or critical COVID-19 with remarkable hemodynamic instability in advanced stages of the disease [11,12], all five cases here presented in early stages of their illness and one was asymptomatic which is in concordance with Thomas J. Oxley et al. work [8]. Similarly, Akshay Avula et al. reported four cases of acute ischemic stroke in association with COVID-19 in the early stage of the disease. The mean age of their patients was 81 years old and due to the underlying comorbidities, the final prognosis was poor [15].

In another case series of six patients, in five patients, ischemic stroke occurred 8–24 days after COVID-19 onset, and in one during the pre-symptomatic phase, suggesting the possibility of COVID-19 associated ischemic stroke occurrence in the early course of the disease [4]. More interestingly, there is a case series of four simultaneously stroke and mild to moderate COVID-19 in the elderly [16].

A unique aspect of our work is the desirable outcome. Except the one who died, others improved with a mean NIHSS of 3.25 and mean mRS of 1.75. It might be influenced by factors as the benign course of COVID-19, presenting in golden time and receiving rtPA, absence of risk factors, and vascular involvement in the form of PRES in one patient. According to a recent meta-analysis, stroke is associated with a 2.5-fold increase in the likelihood of severe COVID-19, with a trend for increased mortality [17]. In the study by Yaghi et al. 63.6% of the stroke patients with active COVID-19 died over hospitalization [18].

Of note, the data on stroke epidemiology has been limited in Iran. The stroke prevalence in Iran is significantly higher than the developed countries especially for stroke in young adults. In regards to risk factors of ischemic stroke, the most common risk factor is hypertension in adults which is similar to all other epidemiologic studies. Compared with stroke in older adults, stroke in young adults is more heterogeneous due to the wide variety of possible etiologies.

Cardio-embolic mechanism comprised the majority of stroke etiology in young adults in Iran in which rheumatic valvular disease is in paramount of importance [19–21].

There are limitations to our study. First, a case series of five patients is not a true representation of the general population in Iran. Additionally, we did not perform the ancillary examination to confirm the pro-inflammatory reactions. Large multicenter studies are required to better understand the association of COVID-19 and juvenile stroke.

Given the increasing cases of COVID-19 worldwide, understanding the relationship between COVID-19 and stroke is a crucial concern. Although our data cannot confirm a causal relationship between COVID-19 and juvenile stroke, it suggest the association between stroke and COVID-19 which might occur in the context of a systemic prothrombotic state.

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