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CASE REPORT

Ischemic stroke associated with novel coronavirus 2019: a report of three cases

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ABSTRACT

Introduction: There is limited evidence about the neurological manifestations of COVID-19 in infected patients. In this report, we describe three patients with ischemic stroke associated with COVID-19 infection.

Methods: We report 3 cases of adult patients with ischemic stroke and novel coronavirus 2019 infection. Case 1 is an 88-year-old female with acute left hemiplegia and right peripheral facial paresis that she had a fever along with stroke symptoms. Case 2 is an 85-year-old female with left hemiplegia and drowsiness who had a weakness, asthenia, and dry cough 3 days before appearing stroke signs. Case 3 is a 55-year-old male with acute Broca's aphasia and right hemiplegia who experience fever and respiratory problems 3 days after admission.

Results: The clinical symptoms of infected patients with COVID-19 have been associated with severe symptoms of ischemic stroke. Two patients were admitted to the ICU. RT-PCR of the oropharyngeal sample was positive in three cases. All patients had the involvement of large cerebral arteries.

Conclusion: The mechanism by which COVID-19 causes ischemic stroke is unknown but it is likely by production inflammatory cytokines or direct infection of cerebral arteries. Therefore, regarding the current situation of the COVID-19 pandemic, it is indispensable that the possible diagnosis of COVID-19 vasculopathy is considered in all ischemic strokes of unclear etiology.

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Introduction

The novel coronavirus 2019 (COVID-19) is a β-coronavirus, which has been revealed in patients with unknown pneumonia in Wuhan, China [1]. The outbreak of COVID-19 has started in China since December 2019 and is rapidly expanding worldwide [2]. The certain receptor to enter the virus into the cell is angiotensin-converting enzyme 2 (ACE2) which, is plentiful on lung alveolar epithelial cells and enterocytes of the small intestine [3]. Therefore, the typical hallmarks observed in patients are respiratory and gastrointestinal symptoms [4]. Over 90% of patients reported fever at the onset of the disease [4]. There is limited evidence about the neurological manifestations of COVID-19 in infected patients. In this respect, Sharifi *et al.* reported concomitant of intracerebral hemorrhage in a patient infected with COVID-19 [5]. Karimi *et al.* described the association of COVID-19 infection with recurrent generalized tonic-clonic seizures in a 30-year-old previously healthy female [6]. Mao *et al.* reported that out of 214 patients infected with COVID-19, 74 cases had neurological symptoms with dizziness and headache as the most common complaints [7]. Ischemic strokes have been reported as a rare consequence of novel coronavirus-related infections. Previous studies reported varicella-zoster virus (VZV), cytomegalovirus (CMV), severe acute respiratory syndrome (SARS), and human immunodeficiency virus (HIV) maybe play a role in the pathogenesis and vasculopathy of ischemic and hemorrhagic strokes [8–9]. Cerebrovascular disease is a common cause of death and disability around the world [10]. There are several risk factors to develop a stroke, including hypertension, diabetes, and hyperlipidemia. Recently, viral infections also were considered as

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risk factors for stroke [9]. In this report, we describe three patients with ischemic stroke associated with COVID-19 infection.

Case presentation

Case1

An 88-year-old female was referred to the emergency department of our hospital, Sari city, Mazandaran province on March 15 2020, due to acute dysarthria, ataxia, impaired orientation, and fever for two days. The patient had a history of hypertension at her medical record. Also, no alcohol consumption or drug abuse was observed. At the admission time, the patient was confused and the first vital signs discovered the following: blood pressure (BP) 160/90 mmHg, heart rate (HR) 95 beats/min, body temperature (T) 38.5.0 °C, respiratory rate (RR) 22 breaths/min, and oxygen (O_2) saturation level of 95% at room air. At the time of hospitalization, the patient was lethargic and a neurological examination showed right peripheral facial paresis (House–Brackmann grade 3), left limb weakness with Medical Research Council (MRC) scale of grade 1 at the upper extremity and grade 2 at the lower extremity. In addition, the patient had horizontal nystagmus, but the size of pupils and spontaneous eye movements were normal. Cerebellar and sensory examinations could not be evaluated due to the decreased level of consciousness. The deep tendon reflexes (DTR) were symmetrically 1-2+, and the cutaneous plantar response was extensor on the left side. No significant findings were found on the cardiopulmonary and abdominal examinations, except for shortness of breath. No skin rashes or bleeding sites were detected after examining the whole body. The results of laboratory test were: serum glucose, 129 mg/dL; white blood cells (WBC), 17.7 × 109/L, neutrophil percentage, 84%; lymphocyte percentage, 8%; C-reactive protein (CRP), 63 mg/L; erythrocyte sedimentation rate (ESR) 86 mm/h; blood urea nitrogen (BUN), 75 mg/dL; creatinine, 1.1 mg/dL; sodium, 142 mmol/L; and potassium, 4.1 mmol/L. Furthermore, liver function and coagulation function tests, electrocardiograms, and electrocardiography were normal. Reverse transcription polymerase chain reaction (RT-PCR) from a throat swab sample was positive for COVID-19. Lung computed tomography (CT) scan showed diffused consolidations and ground-glass opacity (GGO) in both lungs (Figure 1). Brain CT showed low-density lesion at right cerebellar consistent with acute ischemic stroke (Figure 1). The patient was admitted in intensive care unit (ICU) and was intubated due to decreased oxygen saturation and difficulty in breathing after five days of admission. The patient was treated with hydroxychloroquine, lopinavir/ritonavir (LPV/RTV), azithromycin, intravenous immunoglobulin, clopidogrel, and atorvastatin. After three weeks of hospitalization in ICU, the patient became aware of surroundings but needed a mechanical ventilator to breathe. Also, the strength of her muscles did not change. The patient had severe respiratory problems and unfortunately passed away due to respiratory complications after six weeks of hospitalization.

Case 2

An 85-year-old female with a history of diabetic Mellitus and hypertension was admitted to the university hospital in Sari city on 5 April 2020, due to drowsiness and weakness of left-sided limbs. The patient had such complications as impaired memory, poor response, asthenia, and dry cough three days before being referred to the emergency department. Also, the patient had experienced acute hemiplegia and central facial paresis on the left side five-hour before admission. The initial physical examination revealed the following: T, 36.8.0 °C; HR, 70 beats/min; RR, 20 breaths/min; BP, 144/76 mmHg; O_2 saturation, 98%; lethargic; speech disturbance; the equal size of bilateral pupils with reactive to light reflex; central facial paresis, hemiplegia with MRC scale of grade 1 at upper and lower extremities, and Babinski at left side. The score of the National Institutes of Health Stroke Scale (NIHSS) was 22 points. The patient's neck was soft, and there were no signs of meningeal irritation. The patient was admitted to the ICU due to drowsiness. The findings of laboratory test demonstrated: fasting blood sugar, 159 mg/dL; WBC, 5.1 × 109/L, with neutrophil, 80% and lymphocyte 17.9%; CRP, 29 mg/L; erythrocyte sedimentation rate (ESR) 56 mm/h. Moreover, all laboratory findings for the liver, renal, electrolytes, and coagulation functions were normal. Electrodiagraphy (ECG) was normal and the ejection fraction was 45% in echocardiography. Brain CT showed attenuation and effacement at the right hemisphere around the Sylvian fissure (Figure 1). The lung CT prominently showed GGO at the right lower lobe, (Figure 1). RT-PCR from the throat and nasal swab samples were positive for COVID-19. This patient was treated with hydroxychloroquine, LPV/RTV, azithromycin, interferon beta-1a, clopidogrel, and atorvastatin. Besides, subcutaneous insulin was given for controlling her high blood sugar. One week after admission, the patient was intubated and connected to a mechanical ventilator due to respiratory distress. The patient's respiratory and neurological symptoms did not improve after three weeks of hospitalization in the ICU.

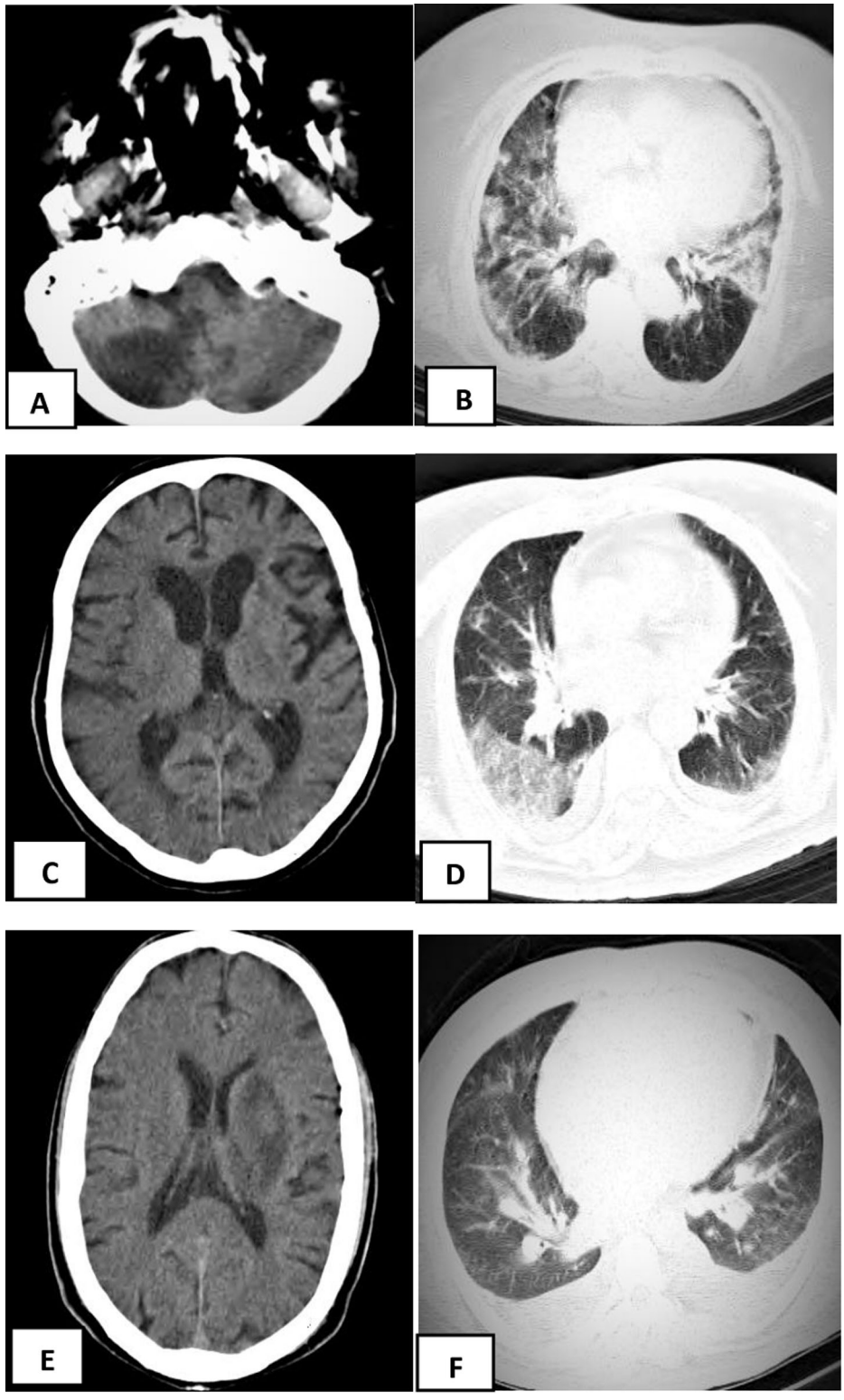

Figure 1. Brain and Lung CT scan of three patients. Imaging of Patient 1 shows low-density at right cerebellar (**A**); grand glass opacity at bilateral lung (**B**); Patient 2 shows attenuation at right hemisphere (**C**); grand grass opacity at the right lower lobe and bilateral pleural effusion (**D**); patient 3 shows low-density at left basal ganglion (**E**); pleural effusion and peripheral grand glass opacity bilaterally (**F**).

Case 3

A 55-year-old male with a history of ischemic heart disease and hypertension was admitted to our hospital on 7 April 2020 with acute weakness in right upper and lower limbs and speech disorder six hours after the start of symptoms. He was a nonsmoker and without a history of drug or alcohol abuse. In the patient's drug history, he had received carvedilol, digoxin, and aspirin. At the time of hospitalization, he complained of productive cough occasionally without fever. General physical examination was unremarkable and vital signs showed O_2 saturation level of 98%; BP, 110/60 mmHg; HR, 66 beats/min; RR, 18 breaths/min; and T, 36.4 °C. Neurological examination revealed Broca's aphasia, right central facial palsy, and right hemiplegia, with muscle force grade 1/5 in the upper extremity and 2/5 in the lower extremity. Routine blood tests were unremarkable, apart from an elevated of WBC (19.5 × 109/L, with neutrophil, 85% and, lymphocyte 7%), CRP, 30; and thrombocytopenia (120000). ECG and echocardiography results demonstrated paroxysmal supraventricular tachycardia (PSVT) and an ejection fraction of 35%, respectively. At the time of hospitalization, Brain CT was unremarkable and lung CT showed mild pleural effusion. Three days later, the patient experienced short of breath, persistent cough, and drowsiness. The lung and brain CT scans were given again. There was hypo-density at left basal ganglion at brain CT and remarkable pleural effusion and GGO bilaterally (Figure 1). The patient's oropharyngeal and nasopharyngeal swabs indicated positive RT-PCR outcomes, which confirmed COVID-19 infection. The patient was treated with aspirin, clopidogrel, carvedilol, digoxin, hydroxychloroquine, LPV/RTV, interferon beta-1a, and azithromycin. After a week, the patient was awake and he had spontaneous breathing but the weakness of right limbs and speech disorder did not change. After two weeks, the patient experienced dyspnea, respiratory complication, and decreased O_2 saturation, again. He was intubated and connected to mechanical ventilator. The brain CT indicated no development of ischemic changes but the lung CT revealed diffuse GGO on both side of the lung.

Discussion

Respiratory tract and gastrointestinal symptoms have been reported as the most obvious clinical symptoms of novel coronavirus 2019 in infected patients [4]. Previous studies reported such symptoms as anosmia, hypomania, and headache as the most prominent neurological manifestations of COVID-19 infection [7]. The present study reported three patients with acute ischemic stroke associated with COVID-19. The diagnoses were confirmed through RT-PCR for COVID-19, along with brain and lung CT scans. The stroke patients described in this study were middle-and old-aged. Also, all patients revealed clinical symptoms of stroke and respiratory problems of COVID-19 infection. The exact time interval between the onset of stroke symptoms and COVID-19 infection was not distinguishable. The first patient was an elderly female who was referred to our hospital with fever and symptoms of a stroke at the same time. The second patient complained of tiredness or fatigue and asthenia, three days before starting the stroke symptoms. The third patient was a middle-aged male who had right hemiplegia, at the admission time. He experienced respiratory tract involvement symptoms after some days of hospitalization and he was later diagnosed with the COVID-19. The brain CT scan of patients suggested cerebral infarction at different parts of the brain (anterior and posterior circulation). Additionally, all patients had shortness of breath and cough and demonstrated GGO on the chest CT scans. Laboratory analyses suggested lymphopenia and elevated CRP levels along with a positive result of the RT-PCR test for COVID-19. Zhai *et al.* reported an elderly patient hospitalized for the weakness of right limbs who was later diagnosed with the COVID-19; the clinical symptoms of this patient was not serious. [10]. In our study, all three patients had severe and life-threatening symptoms compared to the previous report and all of them were admitted to the ICU and connected to the mechanical ventilator. The mechanism of stroke following viral infection is still unclear and debatable. But the virus may directly disturb the vascular wall during the course of infection or indirectly damage the arterial wall *via* the release of inflammatory cytokine. Therefore, both mechanisms may play a role in smooth muscle cell proliferation and platelet aggregation [11]. However, the role of ACE2 in creating neurological symptoms should not be overlooked. The COVID-19 attaches to the ACE2 receptor to invade the cell [7]. It has been hypothesized that binding this virus to the ACE2 receptor can produce pro-inflammatory cytokines in serum, which may stimulate the atherosclerosis process and vasculopathy. Inflammation plays a significant role in the incidence, generation and prognosis of cerebrovascular diseases [10]. In this regard, Huang *et al.* reported the patients admitted to the ICU due to the COVID-19 infection had higher serum levels of inflammatory cytokines [12]. Inflammation might be a factor in creating

atherosclerosis and may affect plaque constancy [10]. However, brain imaging of patients revealed that COVID-19 can affect large arteries resulting in ischemic stroke.

Conclusion

We report three infected patients with COVID-19 associated with ischemic stroke. The mechanism by which COVID-19 causes ischemic stroke is unknown but it is likely by production inflammatory cytokines or direct infection of cerebral arteries. Therefore, regarding the current situation of the COVID-19 pandemic, it is indispensable that the possible diagnosis of COVID-19 vasculopathy is considered in all ischemic strokes of unclear etiology. It is recommended that future research be undertaken in association with COVID-19 and ischemic stroke.

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References

[1] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. N Engl J Med. 2020;382(8):727–728.

[2] CDC. First travel-related case of 2019 novel coronavirus detected in United States. January 21, 2020. Available from: https://www.cdc.gov/media/releases/2020/p0121-novel-coronavirus-travel-case.html

[3] Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. Preprint at bioRxiv. 2020. DOI:10.1101/2020.01.26.919985

[4] Jiang F, Deng L, Zhang L, et al. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545–1549. [PubMed: 32133578].

[5] Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect. 2020;35:100669.

[6] Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: a case report. Iran Red Crescent Med J. 2020;22(3):102828.

[7] Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 inWuhan, China: a retrospective case series study. MedRXiv 2020. DOI:10.1101/2020.02.22.20026500

[8] Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004;251(10):1227–1231.

[9] Nagel MA, Mahalingam R, Cohrs RJ, et al. Virus vasculopathy and stroke: an under-recognized cause and treatment target. Infect Disord Drug Targets. 2010;10(2):105–111.

[10] Zhai P, Ding Y, Li Y. The impact of COVID-19 on ischemic stroke: a case report. Research Square. 2020. DOI:10.21203/rs.3.rs-20393/v1

[11] Shan K, Guo W. Stroke caused by an inflammatory thrombus: a case report. BMC Neurol. 2017;17(1):33.

[12] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506..