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Case Report

Decompressive hemicraniectomy for acute ischemic stroke associated with coronavirus disease 2019 infection: Case report and systematic review

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Received : 24 January 2021
Accepted : 24 February 2021
Published : 24 March 2021

DOI
10.25259/SNI_64_2021

Quick Response Code:

ABSTRACT

Background: Decompressive hemicraniectomy (DH) has been performed for some cases of acute ischemic stroke in patients with coronavirus disease 2019 (COVID-19) infection, but there is little information about the clinical course and outcomes of these patients.

Case Description: We report a case of a 36-year-old woman with COVID-19 infection who developed stroke like symptoms while under home quarantine. Cranial CT scan showed an acute left internal carotid artery (ICA) infarct. She subsequently underwent an emergent left DH. Despite timely surgical intervention, she succumbed to chronic respiratory failure. A systematic review of SCOPUS and PubMed databases for case reports and case series of patients with COVID-19 infection who similarly underwent a DH for an acute ischemic infarct was performed. There were eight other reported cases in the literature. The patients' age ranged from 33 to 70 years (mean 48), with a female predilection (2:1). Respiratory preceded neurologic symptoms in 83% of cases. The ICA was the one most commonly involved in the stroke, and the mean NIHSS score was 20. DH was performed at a mean of 1.8 days post-ictus. Only four out of the nine patients were reported alive at the time of writing. The most common cause of death was respiratory failure (60%).

Conclusion: Clinicians have to be cognizant of the neurovascular complications that may occur during the course of a patient with COVID-19. DH for acute ischemic stroke associated with the said infection was reported in nine patients, but the outcomes were generally poor despite early surgical intervention.

Keywords: Acute ischemic stroke, Coronavirus disease 2019 infection, Decompressive hemicraniectomy, Infarct, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is primarily a respiratory illness that is responsible for the ongoing pandemic around the world.[5] An emerging discovery about COVID-19 is the mounting evidence linking the infection with acute ischemic stroke.[20] A retrospective study of 214 patients with COVID-19 infection from Wuhan, China, showed that 5.7% of the patients with severe infection suffered an acute cerebrovascular event.[18] In fact, there was a 7.5-fold increase in the odds of stroke with COVID-19 compared to patients with influenza.[20] Even more worrisome are the increasing number of reports of acute ischemic stroke in patients with COVID-19 infection who were younger than 50 years old.[23,26]

In the pre-COVID period, patients who had a large-vessel ischemic stroke that caused significant edema and were refractory to medical management would be offered decompressive hemicraniectomy (DH). However, because of the novelty of COVID-19, there is scarce data on whether COVID-19 infection should be factored into the surgical decision-making process for hemicraniectomies, given that severe strokes were typically associated with poor prognosis.[16]

In this paper, we report the case of a 36-year-old woman who underwent DH for an acute infarct in the left internal carotid artery (ICA) distribution several days after being diagnosed with COVID-19 infection. We also review the relevant literature.

CASE DESCRIPTION

A 36-year-old right-handed woman presented with a few days' history of cough, diarrhea, and fever. Medical history was significant for hypertension and polycystic ovary syndrome, for which the patient took anti-hypertensive medications and oral contraceptives. A nasopharyngeal swab showed that the patient was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The patient was prescribed Azithromycin and sent home to quarantine.

On the 8th day of home quarantine, the patient was found to have right-sided weakness and facial droop and was brought to the emergency department 8 h post-ictus. She had sustained wakefulness and was able to localize to pain, and her pupils were equal and briskly reactive to light. She also had hemiplegia and right central facial palsy. The NIHSS score was 25. Cranial CT scan showed a hypodensity at the left ICA territory without midline shift and an Alberta Stroke Program Early CT Score of 0 [Figure 1]. She was admitted to the ICU and started on medical decompression. Admission D-dimer and C-reactive protein (CRP) were elevated.

A 24-h monitoring CT scan showed an increased degree of hypodensity in the left ICA distribution, as well as a midline shift of 7.3 mm. In view of this finding, DH was recommended, but there was no consent. Shortly after, the patient was found to have tachycardia, labored breathing, and decrease in sensorium. She was only able to open her eyes to painful stimuli and withdraw to pain, and her left pupil became dilated. She was intubated, and then brought to the operating room for DH after consent was secured. Postoperatively, the patient's sensorium improved, and she was able to open her eyes to speech and localize to pain. The anisocoria was reversed.

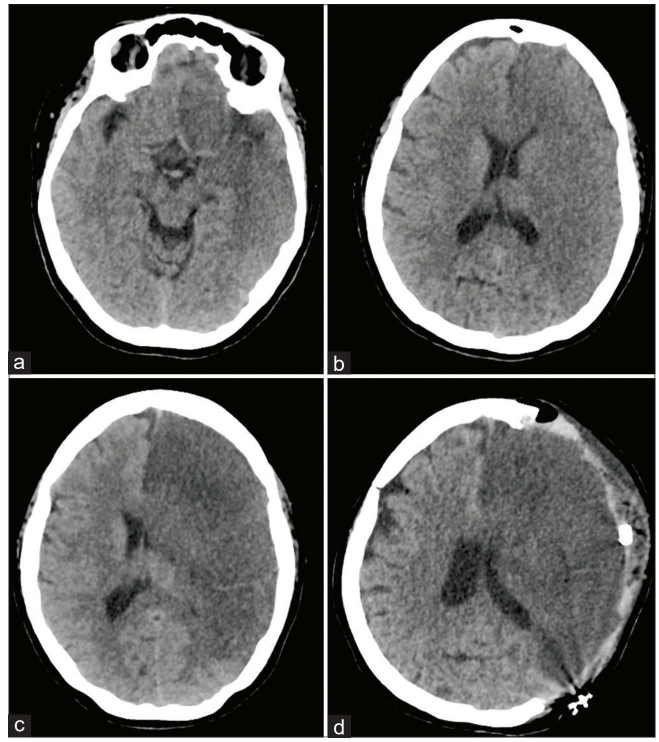

Figure 1: Axial images of initial 8-h cranial CT scans showed a dense left MCA sign (a) and hypodensity in the left ICA distribution (b). 24 h CT scan showed increased degree of hypodensity in the left ICA distribution and midline shift to the left (c). Postoperative CT scan showed a large left-sided craniectomy defect.

However, the patient continued to have fever, tachycardia, and tachypnea despite ventilatory support. Chest radiograph showed bilateral pneumonia with consolidation. The levels of the inflammatory markers D-dimer and CRP were higher than on admission, and ferritin and LDH levels were elevated as well. After 2 weeks, a repeat nasopharyngeal swab showed that the patient was negative for SARS-CoV-2. A tracheostomy was performed.

Over the course of her ICU stay, the patient also developed ventilator-associated *Acinetobacter baumannii* pneumonia and pulmonary tuberculosis. She had persistent desaturation and hypoxia, making it difficult to wean her off ventilatory support. The patient succumbed to chronic respiratory failure 25 days post-ictus.

METHODOLOGY

A systematic search of PubMed and SCOPUS databases was performed using the keywords "hemicraniectomy," "malignant infarct" or "malignant edema," and "COVID." The reference lists of the assessed articles were also searched for relevant studies. All English-language case reports or case series about patients who were diagnosed with COVID-19 infection, developed cerebral infarct, and underwent DH were collected and analyzed. The data collected included demographics, clinical features, imaging results, laboratory parameters, outcomes, and complications.

A total of 22 records were identified through a database search. Of these, 13 articles were excluded after screening the titles and abstracts for relevance to the study. The full text of nine articles was assessed, of which three articles were excluded because they did not meet the inclusion criteria (e.g., no consent for hemicraniectomy). Six studies were included in the final qualitative analysis [Figure 2].

RESULTS

There were nine reported cases of patients with COVID-19 infection and large-vessel ischemic stroke who underwent DH, including the present case [Table 1]. The age of the patients ranged from 33 to 70 years (mean 48), with a female predilection (2:1). Respiratory symptoms preceded neurologic symptoms in 83% (5/6) of the cases where this was reported. The ICA was the most common artery involved in the stroke, and the mean National Institutes of Health Stroke Scale (NIHSS) score was 20. Stroke management included tissue plasminogen activator (tPA) in 33% of cases and thrombectomy in 56%. There was neurologic deterioration before surgery in 67% of the cases, and DH was performed at a mean of 1.8 days post-ictus. Only four out of the nine patients were reported alive at the time of writing, with the longest survivor alive at 28 days post-ictus. The most common cause of death in the series was respiratory failure (60%).

DISCUSSION

COVID-19 infection may primarily be a respiratory disease, but a meta-analysis showed that the incidence of acute ischemic stroke in COVID-19 patients ranges from 0.9 to 2.7%.[29] What is even more alarming are reports of stroke in COVID-19 patients younger than 50 years of age.[16,20,23,24,26,28] Before the COVID-19 pandemic, the average age of a patient with ischemic stroke was 66 (±12) years,[22] but the average age in this series was nearly two decades younger at 48 (±11) years.

It was difficult to determine if the ischemic stroke was incidental or was caused by the SARS-CoV-2 virus, but

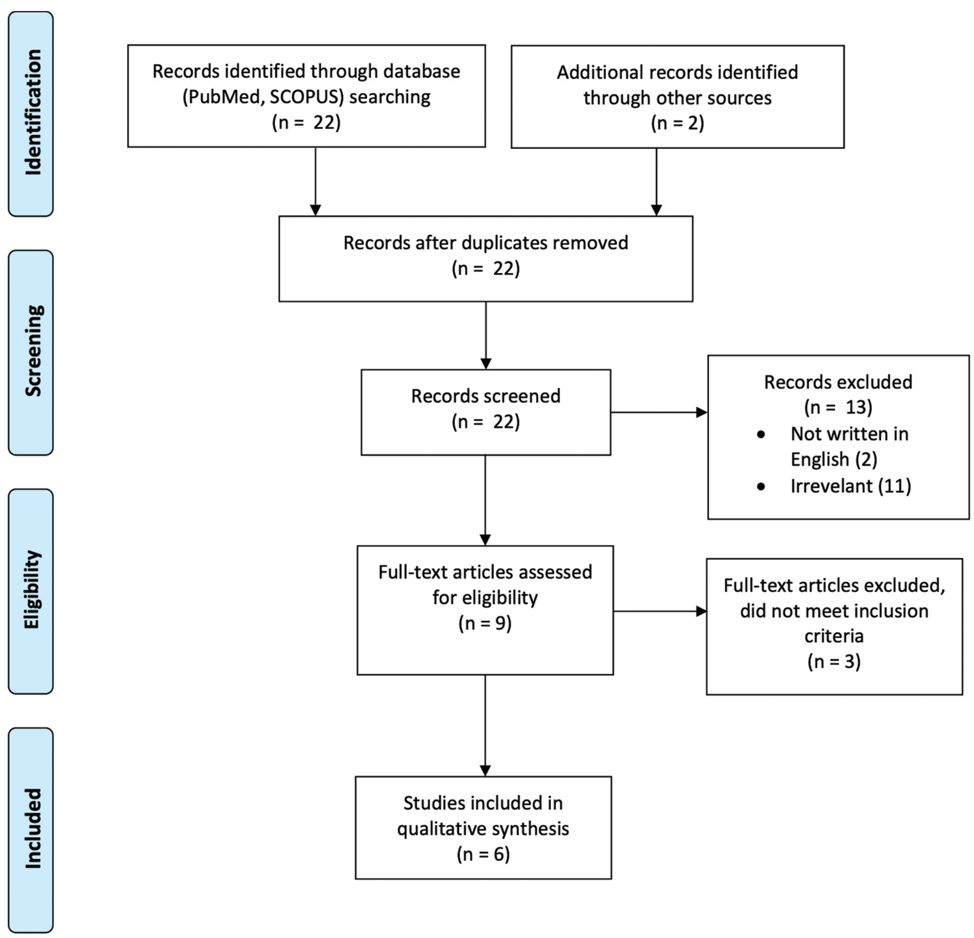

Figure 2: PRISMA flow diagram of the systematic review.

Table 1: Cases of COVID-19 associated ischemic infarct who underwent decompressive hemicraniectomy reported in the literature.

	Liang, 2020			Kananeh, 2020	Oxley, 2020	Roy, 2020	Patel, 2020	Pisano, 2020	Chan, 2020
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age/sex	41/M	51/F	61/M	70/F	44/M	46/F	48/F	33/F	36/F
Clinical presentation	"Stroke," "hypoxia"	Fever, cough, "stroke"	"Stroke"	Fever, SOB, hypoxia	Decreased sensorium, dysphagia, hemiplegia	Cough, confusion, hemiplegia	Cough, dyspnea, fever	Cough, fatigue, fever	Cough, diarrhea, fever
Risk factors for stroke	DM	HTN, DM	DM	None	DM	DM	Obesity, HTN, Hyperlipidemia, drug use, gout	Obesity	HTN, oral contraceptive use
Respiratory preceded neurologic symptoms	NR	NR	NR	Yes	Simultaneous	Yes	Yes	Yes	Yes
NIHSS	23	20	12	28	23	NR	16	15	25
Infarct location	L M1	L ICA	R ICA	R ICA	L MCA	R ICA	R MCA	L ICA	L ICA
Midline shift (mm)	13	10	11	present	NR	present	14	NR	7
Tissue plasminogen Activator	Yes	No	Yes	No	Yes	No	No	No	No
Thrombectomy	TICI 2B	No	TICI 2B	TICI O to 2A	Clot retrieval	No	No	Yes	No
DH post stroke day	1	2	1	2	NR	1	3	2	2
Oxygen requirement	2 liters, nasal cannula	Room air	Room air	MV	NR	MV	High flow oxygen	NR	MV
Inflammatory markers	NR	NR	NR	↑D-dimer ↑CRP ↑Ferritin ↑IL6	↑ D-dimer ↑Ferritin	↑ D-dimer ↑Fibrinogen	↑ D-dimer ↑CRP ↑Fibrinogen	↑ D-dimer	↑ D-dimer ↑CRP ↑Ferritin ↑LDH
Outcome, days post-ictus	Alive, D28	Deceased, D3	Alive, D14	Deceased, NR	Alive, D14	Deceased, D4	Alive, NR; On palliative care	Deceased, D11	Deceased, D25
Complications (if alive); Cause of death (if deceased)		Myocardial infarction	Hemorrhagic conversion of infarct	Acute respiratory distress syndrome		Acute respiratory failure	Worsening respiratory status and septic shock	Sepsis	Chronic respiratory failure

DM: Diabetes mellitus, HTN: Hypertension, SOB: Shortness of breath, ICA: Internal carotid artery, MCA: Middle cerebral artery, MV: Mechanical ventilator, TICI: Thrombolysis in cerebral infarction, DH: Decompressive hemicraniectomy, NR: Not reported several theories have been proposed regarding the causative mechanism.

First, patients with COVID-19 infection were found to have elevated serum levels of circulating D-dimer, a marker of systemic hypercoagulability, and rendering patients prone to a cerebrovascular event.[1] In fact, a D-dimer level greater than 1.6 mg/L may indicate a high possibility of cardioembolic stroke,[7] since it may reflect ongoing thrombus formation within cerebral vessels.[32] In our review, six out of nine patients had elevated D-dimer levels, while this data were not reported in the other three patients. Elevated D-dimer levels in COVID-19 patients increase blood coagulation, thrombin formation, and intravascular fibrin, which may lead to clot formation in large intracranial vessels.[13]

Another proposed mechanism was an exaggerated systemic inflammation or "cytokine storm" brought about by COVID-19 infection.[1,19] The production of cytokines such as interleukin-6, interferon-gamma, and tumor necrosis factor causes the infection of CD4+ T helper cells, monocytes, and central nervous system glial cells, which leads to disruption of the blood–brain barrier and inflammation of the central nervous system.[28] This cytokine surge has been linked with the development of acute cerebrovascular disease.[13]

A third proposed mechanism was the depletion of angiotensin-converting enzyme 2 (ACE2) leading to endothelial dysfunction of the brain. ACE2 has been shown to enhance atherosclerotic plaque stability and has a cardiovascular protective effect.[31] The SARS-CoV-2 virus binds to ACE2 through its spike protein S.[28] By doing so, the virus depletes ACE2 through receptor endocytosis, generating angiotensin II which worsens endothelial and smooth muscle cell function in organs such as the heart and brain, leading to organ damage.[10] Cellular infection with SARS-CoV-2 thus leads to a decrease in ACE2 expression levels which ultimately causes an overall net vasoconstriction, prothrombotic, and pro-inflammatory state in the brain.[26]

Moreover, the accompanying hypoxemia brought about by the infection leads to intracellular acidosis and increases anaerobic metabolism, worsening the cerebral edema, and eventually leading to cell damage and apoptosis.[13] The accumulation of lactic acid causes cerebral vasodilation, swelling of brain cells, interstitial edema, and obstruction of cerebral blood flow, and as the hypoxia continues, cerebral edema increases further.[31] The prolonged hypoxic state brought about by COVID-19 pneumonia worsens the cerebral edema and accelerates cerebral herniation, necessitating a hemicraniectomy. In pre pandemic times, malignant cerebral edema resulting in clinical deterioration usually begins within 48 h post-ictus and reaches its maximum extent between the 3rd and 8th days post-ictus.[6] In a large study of 1301 patients who underwent hemicraniectomy for stroke, 22.1% had surgery within 24 h, 55.8% within 48 h, and 76.8% within 72 h of the onset of stroke, and the ones who underwent the procedure after 48 h had a poorer outcome.[3] In this review series, DH had to be performed between the 1st and 3rd days post-ictus (mean of 1.8 days) due to rapid neurologic deterioration, but the outcome was still poor. This may suggest that the cerebral swelling associated with strokes in COVID-19 patient's progress more rapidly.

All nine patients in this series underwent DH; however, five did not survive and only four were alive at the time of writing, with one of them on palliative care. This translates into a mortality rate of 56%, which is higher than the mortality rates reported in the pre-COVID era. The mortality rate ranged from 8 to 31% in non-randomized prospective case series of patients who underwent DH for malignant hemispheric infarction,[8,14,15,17,25] while a pooled analysis in a randomized controlled trial showed a mortality rate of 22%.[12] In contrast, patients who were managed medically had mortality rates as high as 76–80%,[14,15] suggesting that DH offers a survival benefit. In fact, a recent meta-analysis showed that the benefit of hemicraniectomy extends beyond increasing the odds ratio of survival by a factor of 5, but also increases functional independence by a factor of 2.[27]

Furthermore, the cause of death for all five patients in the series was non neurologic, with respiratory failure being the most common cause. In comparison, non neurologic causes of death only comprise about 20–33%[11,17] of acute-phase mortalities in stroke patients who underwent DH. Neurologic causes such as herniation and cerebral edema were still the main causes of death within this period.[11,17]

Indeed, the preliminary reports of the outcomes of DH for ischemic stroke in COVID-19 patients were dismal despite early intervention, making us wonder if the presence of COVID-19 infection should be factored into the decision to undergo neurosurgical intervention. Some authors have even suggested conservative management of COVID-19 related malignant infarcts because of the poor prognosis.[4,9,21]

Prospective studies with a larger sample size and more comprehensive collection of clinical and laboratory data are essential to establish a prediction model and prognostic effect. Furthermore, the prognostic variables that have been identified in the reported studies used mortality as end points. Other variables may also be relevant in the outcomes of patients, such as pulmonary function ratio, duration of mechanical ventilation, and need for sedation, and larger studies using multivariate analysis would be required.

Given the possible association between COVID-19 and stroke, healthcare workers have to be cognizant of the neurovascular complications that may occur during the course of COVID-19 illness. In the Philippines, patients with mild cases of COVID-19 are advised to quarantine at home or at quarantine facilities; thus, patients and their families must be advised regarding the potential risk for stroke and surveillance for neurologic manifestations so that they can seek medical intervention in a timely manner.

Stroke diagnosis and monitoring may also be challenging in patients with severe COVID-19 infection admitted in the ICU. The dyspnea, air hunger, and physical discomfort of being intubated may require continuous deep sedation and paralysis for these patients. Moreover, deep sedation is recommended for intubated COVID-19 patients because it permits proper lung ventilation in patients with respiratory distress syndrome.[2] Clinicians must be vigilant when managing patients under pharmacologic sedation since it would be difficult to monitor patients' neurologic status, leading to a potential delay in stroke diagnosis. In fact, it would not be surprising if ischemic strokes were under reported in this subgroup of patients.

As the COVID-19 pandemic continues to spread, our understanding on how to approach and treat patients is continuously evolving. Even if COVID-19 is primarily a pulmonary disease, the cases in this series demonstrate that affected patients can develop acute infarcts despite a younger age, and the outcome is generally poor even after neurosurgical intervention.

CONCLUSION

DH for cerebral infarction associated with COVID-19 infection has been reported in nine cases. The operation was performed between the 1st and 3rd days post-ictus (mean 1.8 days), but despite early surgical intervention, the outcomes were generally poor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Chan KI, Salonga AE, Khu KJ. Decompressive hemicraniectomy for acute ischemic stroke associated with coronavirus disease 2019 infection: Case report and systematic review. Surg Neurol Int 2021;12:116.