

Cerebellar Stroke in a COVID-19 Infected Patient. A Case Report

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ABSTRACT

Background: Recent studies have reported that COVID-19 infected patients with stroke, who were often in the older age group, had a higher incidence of vascular risk factors, and more severe infection related respiratory symptoms. These observations provided little evidence to suggest that COVID-19 infection is a potential causative factor for stroke. This report describes a young patient with a cerebellar stroke secondary to COVID-19 infection. **Case presentation:** A 45-year old male presented at a hospital, reporting a two-day history of headache, vertigo, persistent vomiting, and unsteady gait. Physical examination revealed gaze-evoked nystagmus on extraocular movement testing, left-sided dysmetria and dysdiadochokinesia. He was diagnosed with a left cerebellar stroke. An external ventricular drain was inserted, and sub-occipital craniectomy was performed to manage the effects of elevated intracranial pressure due to the extent of oedema secondary to the infarct. He also underwent screening for the COVID-19 infection, which was positive on SARS-CoV-2 polymerase chain reaction testing of his endotracheal aspirate. Blood and cerebrospinal fluid samples were negative. After the surgery, the patient developed atrial fibrillation and had prolonged vomiting symptoms, but these resolved eventually with symptomatic treatment. He was started on aspirin and statin therapy, but anticoagulation was withheld due to bleeding concerns. The external ventricular drain was removed nine days after the surgery. He continued with active rehabilitation. **Conclusions:** Young patients with COVID-19 infection may be more susceptible to stroke, even in the absence of risk factors. Standard treatment with aspirin and statins remains essential in the management of COVID-19 related stroke. Anticoagulation for secondary prevention in those with atrial fibrillation should not be routine and has to be carefully evaluated for its benefits compared to the potential harms of increased bleeding associated with COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, cerebellar stroke, atrial fibrillation

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■ BACKGROUND

Neurological manifestations in COVID-19 infection have been well documented in recent observational studies, ranging from mild symptoms of dizziness to more severe stroke and seizures complications. An early study reported on over a third of COVID-19 patients who had neurological symptoms. Dizziness and headache were the commonest at 16.8% and 13.1% respectively, while stroke occurred less frequently in 2.8% of patients based on that study [1]. Subsequent case series reported that COVID-19 patients with stroke were often in the older age group, had a higher incidence of

vascular risk factors or more severe respiratory symptoms from COVID-19 infection [2, 3]. Such observations suggest that the same risk factors for stroke may be associated with more severe COVID-19 infection, but provide little evidence to support the infection as a direct causative factor for stroke.

On the other hand, young patients with no risk factors, presenting with large vessel ischemic stroke would raise a higher suspicion for COVID-19 infection as a contributory factor to stroke development once other predisposing factors have been excluded [4]. Similar findings of large artery cerebral infarctions were previ-

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ously reported in patients with Severe Acute Respiratory Syndrome (SARS) virus infection [5]. This case report is another example of a young patient without significant risk factors presenting with stroke as the primary manifestation of COVID-19 infection.

■ CASE PRESENTATION

A 45-year-old Bangladeshi male presented at the Emergency Department of Singapore General Hospital, Singapore, giving a two-day history of moderately severe throbbing headache, associated with vertigo, multiple vomiting episodes aggravated by head movements, and unsteady gait. He negated having any visual symptoms, dysarthria, dysphagia, anosmia, and ageusia. He had no fever or respiratory symptoms. He was a smoker, reporting that this was limited to one cigarette a day. No other significant medical history was reported.

Upon admission, his vital signs were stable, and his Glasgow Coma Scale (GCS) was 15. He had mild anisocoria with a 2mm left pupil and 3mm right pupil. Extraocular movement testing revealed hypermetric saccades in all directions, gaze-evoked nystagmus, with a jerky, slow pursuit. The left nasolabial fold was

diminished, but the contractions of the facial muscles were mostly symmetrical. His tongue was central and palatal elevation was normal. Examination of the limbs revealed normal tone, power, reflexes and sensation. There were left-sided dysmetria and dysdiadochokinesia. Examination of the heart, lungs and abdomen were unremarkable. The National Institutes of Health Stroke Scale (NIHSS) score on admission was 2. Computed tomography (CT) of the brain, performed on admission, showed hypodensity with a loss of grey-white differentiation in the left cerebellar hemisphere, with the left middle cerebellar peduncle's involvement and left hemipons. There was a mass effect on the fourth ventricle and crowding of the left foramen magnum region (Figure 1). CT angiography of the major vessels from the level of the aortic arch to the Circle of Willis was performed to evaluate for abnormalities of the vertebral and carotid arteries, with no abnormalities detected. The patient was diagnosed with a left cerebellar infarct.

The following investigations were also performed on admission. A full blood count showed an elevated white blood cell count of $11.97 \times 10^9/L$ with mild lymphopenia ($0.97 \times 10^9/L$). The haemoglobin and platelet counts

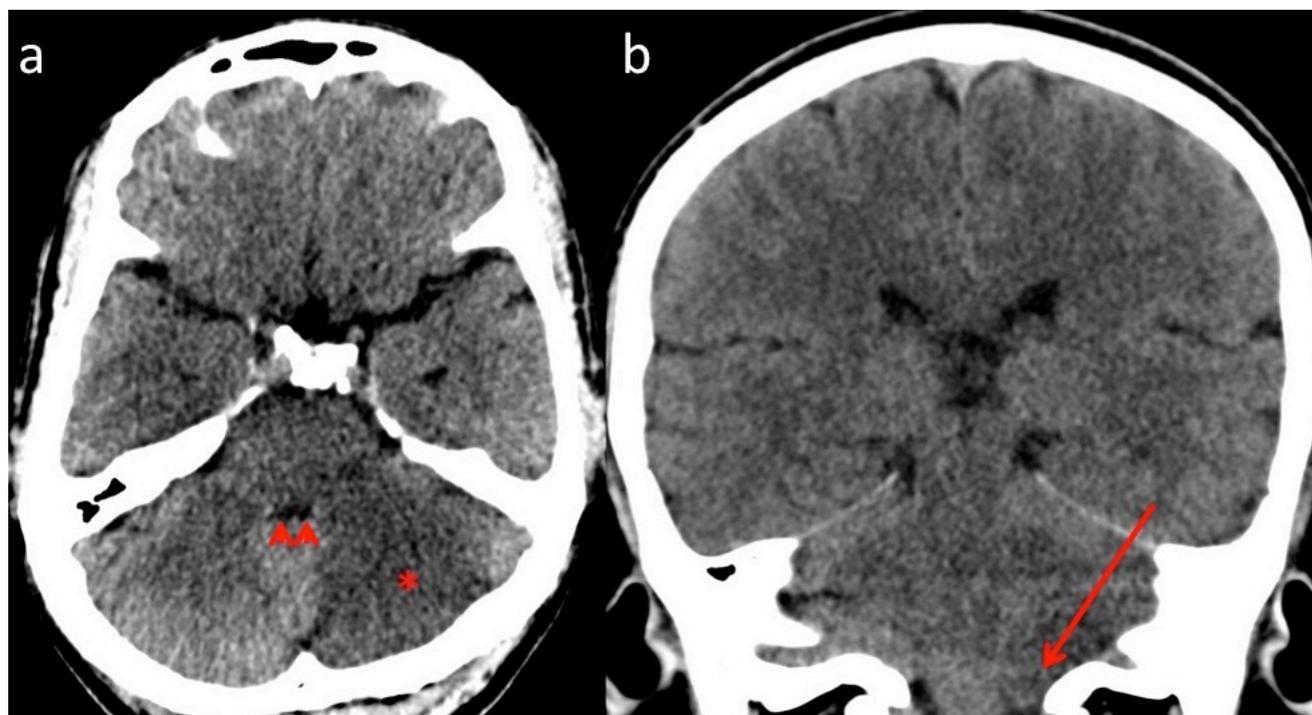


Fig. 1. Axial (a) and Coronal (b) images of an unenhanced CT brain demonstrating an area of hypodensity with loss of grey-white differentiation in the left cerebellar hemisphere (*), extending to involve the left middle cerebellar peduncle, in keeping with an established infarct. There is associated mass effect with mild effacement of the fourth ventricle (arrowheads) and mild left inferior cerebellar tonsillar descent with crowding of the foramen magnum's left side (long arrow).

were normal. C-reactive protein level was 3.5mg/L. D-dimer level was 0.33mg/L Fibrinogen Equivalent Units (FEU). The glycated haemoglobin (HbA1c) measured 6%, and fasting lipid levels were normal. A chest radiograph was reported as normal.

The patient was admitted to the high dependency ward of the hospital for close monitoring on the day of admission. Negative pressure ventilation was started as he had a positive contact history with suspected COVID-19 patients, in his worker dormitory. Oro-nasopharyngeal swabs for SARS-CoV-2 polymerase chain reaction (PCR) testing were not performed to avoid gagging that might cause a further rise in his intracranial pressure. Blood samples were obtained for SARS-CoV-2 IgG serology, which tested positive. The hospital neurosurgeon reviewed the patient. He advised intravenous mannitol 20%, (B.Braun Medical Industries Sdn Bhd, Penang, Malaysia) 100mL, six-hourly, starting on the day of admission, and continued until Day 3 post-admission, and 3% sodium chloride solution to target a sodium level of 140 to 145mmol/L and serum osmolality up to 320 mmol/kg.

On the Day 2 post-admission, the patient became drowsier registering a GCS 13 (E3V4M6). After a neurosurgical consult, he underwent a right frontal external ventricular drain (EVD) insertion and a sub-occipital craniectomy, as an emergency treatment.

Intraoperatively the left cerebellum appeared swollen, herniated and infarcted. Some infarcted left cerebellar tissue had to be removed to reduce the herniation. Postoperatively the patient remained intubated and was sent to the intensive care unit.

The initial EVD level was set at 15cmH₂O above the tragus. He received pressure-controlled ventilation with these initial settings: driving pressure 17cmH₂O, PEEP 5cmH₂O, FiO₂ 30%. His PaCO₂ remained in the range between 35 to 42 mmHg, and pH was normal throughout. When he was more awake, these were quickly weaned to spontaneous ventilation with pressure support of 8cmH₂O, PEEP 5cmH₂O, FiO₂ 25%.

The patient's post-operative recovery was complicated by hypotension requiring thirty hours of intravenous noradrenaline (Laboratoire Aguettant, Lyon, France), 0.02-0.15 mcg/kg/min from Day 2 to Day 4, post-admission, to maintain adequate cerebral perfusion pressure of at least 60mmHg. There was also a new onset of atrial fibrillation with intermittent sinus pauses, the longest lasting twenty-two seconds, which spontaneously reverted to sinus rhythm.

A cardiology opinion was sought, and the arrhythmia was attributed to dysautonomia from brainstem involvement of the stroke.

Endotracheal (ET) aspirates were collected on Day 2 and Day 3, post-admission; blood and cerebrospinal fluid (CSF) samples were collected on Day 4, post-admission, for SARS-CoV-2 PCR testing.

The ET aspirate tested positive for SARS-CoV-2 virus, but results were negative for the blood and CSF samples.

The patient had persistent cyclic vomiting even after the craniectomy. These were sudden episodes with no associated symptoms of headache or abdominal distension. Gastric residual volume was minimal. The symptoms were alleviated with intravenous ondansetron (Intas Pharmaceuticals Ltd, Ahmedabad, India) 4mg eight hourly and intravenous metoclopramide (Yung Shin Pharmaceutical Ind. Co. Ltd, Taichung, Taiwan) 10mg, eight hourly, starting on Day 5 post-admission. The symptoms resolved after nine days.

Two days after the craniectomy, the patient became drowsier again, recording a GCS=9, E2V1 (intubated) M6, and had weakness in his left upper and lower limbs. The repeated brain-CT showed no change in the size of the infarct or evidence of haemorrhagic conversion, but there was a slight increase in both lateral ventricles' size. The EVD level was lowered from 10 to 5cmH₂O; the sodium level target was raised to between 145 and 150mmol/L to reduce cerebral oedema. His condition continued to improve and was eventually extubated after two days. The EVD was safely removed on day nine post-craniectomy.

The following investigations were performed on Day 8 post-admission to evaluate potential causes of stroke. Transthoracic echocardiography (TTE) showed an average left ventricle ejection fraction of 55 to 60%, with no regional wall motion abnormality. The left atrium (LA) size was normal, with an LA volume of 19.56ml/m². No valvular abnormalities or intracardiac thrombi were detected. A thyroid function test, done on first-day post-admission was normal. Extensive investigations for thrombophilia were performed on the sixth-week post-admission. These included: Anti-cardiolipin IgM & IgG antibodies negative, Lupus anticoagulant negative, Protein C 125%, Protein S 87%, Antithrombin III 111%, Homocysteine 6.7 micromol/L. Autoimmune markers, including Antinuclear antibody (ANA), Anti Myeloperoxidase (MPO) antibody, Anti Proteinase 3 (PR3) antibody, and Anti-double-stranded DNA (ds-

DNA) antibody, were all negative.

Based on these results, the patient was deemed unlikely to have any underlying thrombophilia or autoimmune diseases contributing to stroke. The patient was started on long term oral aspirin (Reckitt Benckiser Healthcare Ltd, Hull, United Kingdom) 100mg daily and atorvastatin (manufactured by Pfizer Pharmaceuticals LLC, Vega Baja, Puerto Rico) 40mg daily for secondary prevention starting on Day 10 post-admission.

At the time of writing, he remained well and was actively participating in rehabilitation before eventual discharge to a community recovery facility.

■ DISCUSSION

COVID-19 related stroke is thought to be due to multiple factors including coagulopathy and endothelial dysfunction, features that are increasingly seen as hallmarks of the COVID-19 infection. Coagulopathy is seen mainly in patients with more severe infection [6, 7]. However, the prothrombin time, D-dimer and platelet levels were normal in our patient. The present patient's symptoms would suggest an aetiology with the central nervous system's more direct involvement rather than complications of a severe systemic infection. A more plausible explanation should include the virus' ability to target its effects on the brain without affecting the rest of the body.

The neurotropism of coronaviruses has been well recognised. A recent literature review on the expression of angiotensin-converting enzyme 2 (ACE2) receptors in the cerebral vasculature, neurons, astrocytes and oligodendrocytes, as well as localisation of ACE2 receptors in the olfactory bulb and other areas of the brain, provided the basis for the possible mechanisms of neuro-invasion and stroke development secondary to COVID-19 infection. These include how the virus crosses the blood-brain barrier (BBB) via retrograde neuronal transport along the sensory and olfactory nerves, or through the infection of macrophages and host cells that pass through the BBB. Infection of the vascular endothelium also causes inflammation and vascular injury, increasing the BBB permeability and facilitating the virus's entry [8].

The pathogenesis of stroke following neuro-invasion of the virus should be explained with an understanding of the renin-angiotensin system (RAS). The RAS is a complex system with important physiological functions, including fluid and electrolyte balance, blood

pressure and cardiovascular homeostasis. In particular, Angiotensin II (ATII) has been implicated in lung injury, leading to severe respiratory failure in COVID-19 patients [9]. Although the BBB insulates the brain from circulating angiotensin effects, the brain has a local independent RAS with all the "classical" RAS components and can synthesise angiotensin. Like lung injury, it is postulated that ischemic stroke results from the effects of ATII, causing vasoconstriction of cerebral vessels and increasing inflammation and oxidative stress in the brain parenchyma. Under normal circumstances, the activation of an alternative axis comprising ACE2-mediated cleavage of ATII to angiotensin (1-7) binds to the Mas receptor, would counter the effects of ATII. This results in vasodilation, anti-inflammatory and antioxidant responses. The ACE2-AT (1-7)-Mas pathway has also demonstrated further benefits of improved angiogenesis, anti-thrombotic activity, and increased stability of atherosclerotic plaques. These protective effects against cerebral ischemia are reduced in COVID-19 infected patients due to the downregulation of ACE2 receptors [10].

The protracted vomiting in our patient was initially attributed to the cerebellar stroke's effects, including a raised intracranial pressure and compression on the fourth ventricle where the area-postrema, i.e. the vomiting centre, is located. However, it would not explain why the vomiting persisted even after decompressive craniectomy. An old experimental model on coronavirus infection in pigs has suggested that vomiting may be induced by a viral infection of the neurons in a few target-tissues, including the brainstem. The vomiting centre receives impulses from infected neurons and triggers vomiting once sufficient afferent stimuli have been reached. This may explain the persistent vomiting in our patient [11].

Anticoagulation therapy is essential for secondary prevention of stroke in patients with atrial fibrillation. The risk of recurrent stroke in our patient was 2.2% per year based on a CHA₂DS₂-Vasc score of 2; whereas the HAS-BLED score of 1 indicated risk of 1.02 bleeds per 100 patient-years. This should be carefully considered in our patient due to large infarct with mass effect in the posterior fossa, of which a haemorrhagic event would be disastrous. Neuroimaging studies have reported more haemorrhagic strokes in COVID-19 infected patients who received therapeutic or prophylactic anticoagulation [12, 13]. It is important to recognise that post-stroke cardiac arrhythmias can occur. Two pro-

spective studies reported 25.1% and 29.5% incidence of cardiac arrhythmias, respectively in the first 48 to 72 hours after a stroke. The incidence of slow atrial fibrillation was 4.8% and 2.7%; and the sinoatrial block was 1.6% and 0.6% respectively [14, 15]. Also, it has been reported that patients with lone atrial fibrillation, without any cardiovascular risk factors, and with normal left atrial volume, did not have an increased risk of stroke compared to the general population in a 30-year follow up period [16]. Our patient had an average baseline electrocardiogram and a TTE which did not show any left atrial enlargement or valvular abnormalities. The atrial fibrillation started after surgery and reverted to normal sinus rhythm after a day, with no further episodes during his stay. The overall assessment suggested that atrial fibrillation was a consequence rather than the cause of the stroke.

Furthermore, extensive investigations were done to rule out underlying thrombophilic conditions, as evident by negative antiphospholipid antibodies, autoimmune markers, and typical coagulation factors. After careful consideration and discussion between neurologists, a decision was made to withhold anticoagulation due to the more significant concern of haemorrhagic complications due to the large infarct size and tight posterior fossa requiring decompression craniectomy initially. As we gained more knowledge of this disease, we felt that coagulopathy associated with COVID-19 infection varies between patients due to disease severity. Hence, the criteria for selecting patients who may benefit from anticoagulation in the acute setting and the duration of anticoagulation in the longer term remains uncertain. We would recommend a close follow-up for these patients after they have recovered from COVID-19 infection until more literature is available on the disease's long-term consequences. The patient received aspirin and atorvastatin treatment. In addition to treatment for stroke, statin therapy's potential benefits in COVID-19 infection have been widely discussed in recent literature, including its anti-inflammatory, anti-thrombotic and immunomodulatory properties [17, 18]. An ongoing trial is being conducted to evaluate aspirin's potential protective effects in COVID-19 patients (ClinicalTrials.gov Identifier: NCT04365309).

COVID-19 specific therapies such as remdesivir and dexamethasone in COVID-19 related stroke remains uncertain because indications for their use based on published studies include patients with lower respiratory tract infection who had poor oxygen saturation and

required mechanical ventilation [19, 20]. Moreover, previous trials on steroids' utility in acute stroke have demonstrated no evidence of significant benefits [21]. Our patient had a primary neurological insult rather than respiratory compromise secondary to COVID-19 infection. Hence none of these additional therapies was offered.

■ CONCLUSION

We have reported a COVID-19 related cerebellar stroke in a young patient. Absence of typical characteristics and risk factors described in the literature in our patient's case gives greater credence to COVID-19 infection as an independent risk factor for stroke. Aspirin and statins are the mainstays of treatment, while anticoagulation requires careful consideration due to the increased risk of intracranial bleed associated with COVID-19 infection. Future studies should explore the role of additional therapies, including antiviral treatment for COVID-19 related stroke.

■ CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interests.

■ CONSENT FOR PUBLICATION

Consent obtained from the patient for case report publication.

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