Characteristics and clinical course of Covid-19 patients admitted with acute stroke

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Dear Sirs,

Covid-19 infection has been associated with a predominant prothrombotic state causing venous and arterial thrombosis [1]. Although cerebrovascular complications were reported in 0.8% and in 5.7% of the patients with non-severe and severe Covid-19 disease [2], respectively, they were associated with 2.5-fold increased odds of severe disease in patients with Covid-19 infection [3]. Previous case reports or case series described patients with Covid-19 infection who developed acute stroke [4–12]. Here, we describe the clinical features, neuroimaging and laboratory findings of a case series of patients with Covid-19 infection consecutively admitted to our hyper-acute stroke unit (HASU), Charing Cross Hospital, Imperial College Health Care NHS Trust (ICHT) with acute stroke via the acute stroke pathway. From the 1 March to 30 April 2020, eight acute stroke patients who tested positive for Covid-19 were consecutively admitted to our HASU. Seven out of eight patients suffered an ischemic stroke, with one patient with a haemorrhagic stroke. The median age of our patients was 74 years old (IQR 11.8), and the median NIHSS on admission was 8.5 (IQR 6.3) (Table 1). Our patients developed the symptoms of stroke after a median interval time of 7 days (IQR 10.5) after the onset of their Covid-19 infection. Of note, three patients

out of eight showed the neurological symptoms of stroke at the same time as the symptoms of the Covid-19 infection. In the seven patients with ischemic stroke, the majority were in the anterior circulation ($n = 6$). Large vessel occlusion or floating thrombus in a large vessel was seen in three patients (Fig. 1). Multiple ischemic infarcts were documented in 5 cases out of 7 of which three patients had bilateral lesions. The size of the infarct was classified as small in four cases [13]. One patient (no. 7) was treated successfully with intravenous thrombolysis with tissue plasminogen activator (t-PA) at 3 h and 15 min after the onset of his symptoms. After 24 h, his NIHSS dropped from 8 to 3 and he was discharged after three days with no neurological symptoms and being functionally independent (mRs 0). Table 2 shows the laboratory and radiologic findings on admission for our patients. Most of our patients had elevated levels of fibrinogen, D-dimer and C-reactive protein. In three out of the four, the patients with severe Covid-19 lymphocytopenia were present while one patient (no. 3) showed an abnormal elevated lymphocyte count in the context of chronic lymphocytic leukemia.

Our case series provided descriptive data on patients with Covid-19 disease that developed acute stroke and were admitted to our HASU via the acute stroke pathways. A recent WSO survey across multiple countries including UK, Italy, Belgium, Greece, Iran, Chile and Colombia has documented that the Covid-19 pandemic has affected the stroke care with a significant fall in the number of stroke admissions, up to 80%, during the COVID-19 outbreak [14]. Moreover, preliminary data suggested that a smaller proportion of patients with milder stroke symptoms presented to hospital during the COVID-19 pandemic [15] due to fears of infection. The median NIHSS on admission of our patient sample was 8.5 suggesting that these more severe symptoms cannot be ignored by patients or family members.

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Table 1 Clinical characteristics of the eight patients with acute stroke

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years), sex	63, F	83, M	88, M	77, M	71, M	55, M	79, M	70, M
Onset of Neurologic syndrome	Concomitant with fever and dyspnea	11 Days after fever and dyspnea	12 Days after fever, malaise, dyspnea	Concomitant with dyspnea and cough	1 Day before dyspnea and tachypnea	10 Days after cough and anosmia	After 7 Days of cough and fever	Concomitant with fever and cough
Severity of COVID infection	Severe	Severe	Severe, developed ARDS	Severe	Moderate	Moderate	Moderate	Moderate
Type of stroke; TOAST classification ^a	Ischemic stroke with small lesions in the anterior circulation; undetermined etiology for incomplete evaluation	Ischemic stroke with small lesions in the anterior circulation; cardioembolic	Ischemic stroke with a small lesion in the posterior circulation; cardioembolic	Ischemic stroke with a medium lesion in the anterior circulation; cardioembolic	Ischemic stroke with a medium lesion in the anterior circulation; undetermined etiology for incomplete evaluations	Haemorrhagic stroke likely hypertensive	Ischemic stroke with small lesions in the anterior circulation; undetermined etiology for incomplete evaluations	Ischemic stroke with a medium lesion in the anterior circulation; cardioembolic
Comorbid conditions	Peripheral vascular disease, ischemic coronary artery disease, hypertension	New onset of Atrial fibrillation		Prostate cancer, known atrial fibrillation, previous intracranial haemorrhage, COPD, hypertension	Neuroendocrine tumor in the colon, diabetes type 2, smoking, hypertension	Hypertension, smoking	Diabetes type 2, Hypercholesterolemia, previous TIAs, hypertension	Diabetes type 2, atrial fibrillation, coronary artery disease
NIHSS on admission and signs/symptoms of stroke	9; neglect, dysphasia, left arm paresis	19; dysphasia, right hemiplegia, sensory deficit, gaze preference, facial droop	3; facial droop, right hemiparesis	13; dysarthria, right hemiparesis	12; right hemiparesis, right hemiparesis, dysphasia, dysarthria	2; right arm paresis and ataxia	8 and 3 after 24 h; dysphasia, right arm paresis, sensory deficit	7; dysphasia, inattention and dysarthria
Brain scan results	Multiple and Bilateral infarcts	Multiple infarcts; floating thrombus in the left ICA	Single infarct	Multiple and bilateral infarcts	Multiple infarcts with hemorrhagic transformation type PH1; floating thrombus in the left ICA	Small intracranial haemorrhage in the left external capsule	No acute infarct on first CT; 24 h MRI showed multiple and bilateral infarcts with hemorrhagic transformation type HI-1	Single infarct with M1/M2 junction large vessel occlusion

Table 1 (continued)

Treatment and outcomes	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
	Received 14 days of Aspirin 300 mg followed by Clopidogrel 75 mg; discharged at home after 7 days with mRs of 3	Received LMWH; still inpatient with mRs of 5	Received 14 days of Aspirin 300 mg followed by Apixaban; still inpatient with mRs of 1	Received Apixaban; discharged at home after 26 days with mRs of 3	Received LMWH; still inpatient with mRs of 1	Received antithrombotic medications; discharged at home after 6 days with mRs of 0	Received iv. Alteplase and 14 days of Aspirin 300 mg followed by Clopidogrel 75 mg; discharged at home after 3 days with mRs of 0; re-admitted after 30 days with a new TIA	Received 14 days of Aspirin 300 mg followed by Clopidogrel 75 mg; still inpatient with mRs of 3

F female, M male, NIHSS National Institutes of Health Stroke Scale, mRs modified Rankin Scale, ICA internal carotid artery, LMWH low molecular weight heparin, TIA transient ischemic attack

^aTOAST Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification applied for ischemic stroke only

Previous studies described the clinical characteristics and course of acute stroke in patients with Covid-19 disease in different healthcare systems compared to ours [4, 16]. Compared to the case series of Oxley et al. [4], most of our patients with ischemic stroke had multiple and small ischemic lesions on the brain scans. Interestingly, as also documented in the case series of Avula et al. [17], we showed three patients with acute stroke as a presenting symptom.

The presence of Covid-19 infection has been associated with a predominant prothrombotic state [1] affecting the fibrinolysis and regulated by various pro-inflammatory cytokines [18].

In our case series, the severe Covid-19 patients were commonly associated with markedly elevated D-dimer, high fibrinogen and elevated APTT levels. This is in line with previous studies suggesting a more pronounced microvascular thrombosis associated with Covid-19 than those induced by non-SARS-CoV2 [19].

As the inflammatory processes have fundamental roles in stroke in either the aetiology and pathophysiology of cerebral ischemia [20], the presence of Covid-19 infection could be a factor in the genesis or worsening of stroke in addition to the potential risk of cardioembolic stroke due to ACE-2 expression in the heart and subsequent cardiac dysfunction [21].

Taken together, our case series highlights the importance of investigating the role of the Covid-19 in the aetiology and pathophysiology of the cerebrovascular disease as a complication of the disease. Viral infections can trigger stroke with different mechanisms that depend on the associated pathogen and host characteristics. Varicella zoster virus (VZV) is responsible for a distinctive vasculopathy involving both large and small arteries [22], while human immunodeficiency virus (HIV) can cause brain large vessel vasculopathy [23]. Data acquisition of larger case series is urgently needed to investigate the potential causative association between Covid-19 and stroke. We believe that, if proven, this would emphasize the importance of early detection of stroke symptoms in Covid-19 patients to allow better identification of those patients who could benefit from reperfusion therapy. In conclusion, we believe that our case description provides further evidence of the heterogeneous neurological complications associated with SARS-CoV-2. Future researches and data acquisition are needed to characterize the casual association and the clinical pattern of new cases of acute stroke observed in the context of Covid-19 pandemic.

Fig. 1 Case 5. **A** CT angiography demonstrates lobulated soft tissue plaque at the left common carotid artery bifurcation which involves the origin of the left internal carotid artery, causing approximately 50% narrowing of the left ICA origin and in keeping with a floating thrombus. The chest XR shows diffuse bilateral air space opacifications. Case 2. **B** CT angiography illustrates a mixture of soft tissue and calcified mural plaque with an intraluminal tail of thrombus

extending into the Internal Carotid Artery. The Chest CT shows bilateral predominantly peripheral interstitial and airspace opacifications as well as bronchocentric opacities predominantly in the lower lobes. Case 8. **C** CT angiography demonstrates acute left middle cerebral artery M1/M2 junction occlusion, and the MRI brain shows acute infarct of the left anterolateral temporal lobe. The chest XR shows bilateral peripheral predominant multiple opacities

Table 2 Radiological and laboratory findings of the eight patients with acute stroke

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Chest XR/CT results	Bilateral consolidations with small pleural effusions	Multifocal bilateral GGO	Multifocal bilateral GGO and bilateral pleural effusions	Unilateral consolidation	Multifocal bilateral GGO	No abnormalities	Multifocal, Unilateral GGO	Multifocal, Bilateral GGO
White blood cell count ($4.2\text{--}7.0 \times 10^9/\text{L}$)	5.6	5.1	27.4	7.2	9.5	6.5	4.8	11.4
Lymphocyte count ($1.1\text{--}3.6 \times 10^9/\text{L}$)	0.6	0.7	18.9	0.7	1.8	1.2	1.1	1.8
Platelet count ($130\text{--}370 \times 10^9/\text{L}$)	132	376	225	214	590	232	148	634
CRP (<5.0 mg/L)	8.4	213.4	279.2	96.2	44.3	98	18.6	80.7
Fibrinogen ($1.90\text{--}4.30$ g/L)	4.21	7.59	9.82	4.96	5.26	4.89	5.17	7.8
APTT (seconds) ($25\text{--}35$)	> 180	74.8	32.3	38.8	30.3	24.7	30.2	28.6
Prothrombin time (seconds) ($12.8\text{--}17.4$)	13.0	18.1	18.7	19.2	14.8	11.8	13.9	14
D-Dimer level (<500 ng/mL)	9709	1256	> 2000	3846	1557	—	—	5952

GGO ground-glass-opacity

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Compliance with ethical standards

Conflicts of interest Lucio D'Anna, Joseph Kwan, Zoe Brown, Omid Halse, Sohaa Jamil, Dheeraj Kalladka, Marius Venter, Soma Banerjee have no conflict of interest.

Ethics approval This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent of subjects was not needed as the data collected for the study were information collected as part of the routine care, and only de-identified data were used in the research.

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