

LETTER

Characteristics of ischaemic stroke associated with COVID-19

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is associated with coagulopathy causing venous and arterial thrombosis.^{1,2} Recent data from the pandemic epicentre in Wuhan, China, reported neurological complications in 36% of 214 patients with COVID-19; acute cerebrovascular disease (mainly ischaemic stroke) was more common among 88 patients with severe COVID-19 than those with non-severe disease (5.7% vs 0.8%).³ However, the mechanisms, phenotype and optimal management of ischaemic stroke associated with COVID-19 remain uncertain. We describe the demographic, clinical, radiological and laboratory characteristics of six consecutive patients assessed between 1st and 16th April 2020 at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, with acute ischaemic stroke and COVID-19 (confirmed by reverse-transcriptase PCR (RT-PCR)) (table 1). All six patients had large vessel occlusion with markedly elevated D-dimer levels ($\geq 1000\mu\text{g/L}$). Three patients had multiterritory infarcts, two had concurrent venous thrombosis, and, in two, ischaemic strokes occurred despite therapeutic anticoagulation.

PATIENT 1

A 64-year-old man presented 10 days after COVID-19 symptom onset (cough, breathlessness, fever, myalgia and poor appetite), with respiratory failure warranting intensive care unit admission. *Mycoplasma pneumoniae* infection was treated with clarithromycin. On day 15, he developed mild left arm weakness and incoordination. MRI confirmed intradural left vertebral artery occlusion and acute left posterior inferior cerebellar artery territory infarct with petechial haemorrhage (online supplementary figure S1A). D-dimer was $>80\,000\mu\text{g/L}$. He received aspirin and clopidogrel. On day 19, he developed bilateral pulmonary embolism, treated with therapeutic low molecular weight heparin (LMWH). On day 22, he developed acute bilateral incoordination and right homonymous hemianopia; MRI brain showed extensive acute posterior cerebral artery territory infarction (online

Table 1 Demographic, clinical, radiological and laboratory findings

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|--|---|--|---|---|---|
| Demographic characteristics | | | | | | |
| Age, years | 64 | 53 | 85 | 61 | 83 | 73 |
| Sex | Male | Female | Male | Male | Male | Male |
| Medical history | Nil | Hypertension, diabetes, mitral valve replacement, atrial fibrillation, heart failure with a permanent pacemaker | Hypertension, hypercholesterolaemia, atrial fibrillation, ischaemic heart disease, prostate cancer (Gleason Score 4+5) | Hypertension, stroke, chronic leg ulcers | Hypertension, diabetes, ischaemic heart disease, smoking and alcohol consumption | Gastric carcinoma (resected), benign essential tremor |
| Symptoms at COVID-19 disease onset | Cough, shortness of breath, fever, myalgia, loss of appetite | Malaise, dry cough, shortness of breath, fever | Cough | Fever, cough, shortness of breath, tachypnoea | Fever, cough, shortness of breath, fatigue | Shortness of breath, tachypnoea |
| Initial treatment | Antibiotics, oxygen therapy | Supportive | Supportive | Antibiotics | Antibiotics, oxygen therapy | Antibiotics, oxygen therapy |
| Days from COVID-19 symptom onset to ischaemic stroke symptom onset | 15 | 24 | 10 | -2 (stroke preceded COVID-19 symptoms by 2 days) | 15 | 8 |
| Clinical symptoms of ischaemic stroke | Word-finding difficulties, bilateral incoordination, right homonymous hemianopia | Acute confusion, incoordination, reduced consciousness (GCS 13/15) | Dysarthria, right facial droop and right-sided weakness | Dysarthria, left facial droop and left-sided weakness | Dysarthria, left facial droop, left-sided weakness and left-sided sensory inattention | Aphasia, right facial droop and right-sided weakness |
| ICU admission and disease severity | | | | | | |
| Days from COVID-19 symptom onset to ICU admission | 14 | 25 | Did not go to ICU | Did not go to ICU | Did not go to ICU | Did not go to ICU |
| COVID-19 disease severity | Severe | Critical | Moderate to severe | Moderate | Severe | Severe |
| Laboratory findings on the day of first or only ischaemic stroke event | | | | | | |
| Haemoglobin (g/L) | 119↓ | 94↓ | 128↓ | 126↓ | 121↓ | 142 |
| White cell count (/mm ³) | 6750 | 23 050↑ | 5080 | 8970 | 11 030↑ | 7300 |
| Differential count (/mm³) | | | | | | |
| Neutrophils | 5810 | 19 200↑ | 4440 | 6390 | 8330↑ | 5800 |
| Lymphocytes | 470↓ | 2070 | 402↓ | 1310 | 1630 | 890↓ |
| Monocytes | 370 | 1660↑ | 180↓ | 900 | 830 | 470 |
| Platelet count (/mm ³) | 305 000 | 254 000 | 173 000 | 408 000↑ | 197 000 | 403 000↑ |
| Albumin (g/L) | 28↓ | 28↓ | 33↓ | 31↓ | 32↓ | 32↓ |
| Alanine aminotransferase (U/L) | 137↑ | 27 | 32 | 24 | 37 | 75↑ |
| Bilirubin ($\mu\text{mol/L}$) | 11 | 29↑ | 17 | 13 | 11 | 10 |
| Lactate dehydrogenase (U/L) | 654↑ | 664↑ | 461↑ | 444↑ | 353↑ | 439↑ |
| Creatinine ($\mu\text{mol/L}$) | 57 | 75 | 77 | 107 | 100 | 68 |
| EGFR (ml/min/1.73 m ²) | >90 | 74 | 87 | 63 | 64 | >90 |
| High-sensitivity cardiac troponin I (pg/ml) | 9 | 42↑ | 32↑ | 30↑ | 66↑ | 8 |
| Prothrombin time (s) | 12.5↑ | 34.4↑ | 11.3 | 10.9 | 11.7 | 12.3↑ |
| International normalised ratio (INR) | 1.14 | 3.6↑* | 1.03 | 0.99 | 1.07 | 1.13 |
| Activated partial-thromboplastin time (APPT) (s) | 35 | 41↑* | 33 | 24↓ | 30 | 32 |
| APPT ratio | 1.1 | 1.3↑ | 1 | 0.8 | 1.0 | 1 |

Continued

Table 1 Continued

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|--|--|---|---|---|--|--|
| Fibrinogen (g/L) | 9.5 ↑ | 7.03 | 5.3↑ | 4.63↑ | 4.96↑ | – |
| D-dimer (µg/L) | >80 000 ↑ | 7,750↑ | 16,100↑ | 27,190↑ | 19,450↑ | 1,080↑ |
| Serum ferritin (µg/L) | 4927 ↑ | 1,853↑ | 1,027↑ | 1,167↑ | | 655↑ |
| High-sensitivity C reactive protein (mg/L) | 305.4 ↑ | 150.1↑ | 161.2↑ | 12.8 | 27.7↑ | 179.9↑ |
| Antiphospholipid antibodies: | Medium titre IgM aCL | IgG and IgM aCL and aβ2GP1 | IgG and IgM aCL and aβ2GP1 | IgG and IgM aCL | IgG and IgM aCL and aβ2GP1 | IgG and IgM aCL and aβ2GP1 |
| Anticardiolipin (aCL) | IgG aCL negative | negative | negative | negative | negative | negative |
| Anti-β2-glycoprotein-1 (aβ2GPI) | Low titre IgG and IgM aβ2GPI | | | | | |
| Lupus anticoagulant | Positive | Positive | Negative | Positive | Positive | Positive |
| Imaging features | | | | | | |
| Brain (see online supplementary figure S1s and S2) | MRI including diffusion-weighted and susceptibility-weighted imaging showed acute left vertebral artery thrombus and acute left posterior-inferior cerebellar artery territory infarction with petechial haemorrhagic transformation. 7 days later, diffusion-weighted MRI showed bilateral acute posterior cerebral artery territory infarcts despite therapeutic anticoagulation | Non-contrast CT showed acute right parietal cortical and left cerebellar infarct with mass effect and hydrocephalus, despite therapeutic anticoagulation | Non-contrast CT showed hyperdensity consistent with thrombus in the left posterior cerebral artery and acute infarction in the left temporal stem and cerebral peduncle | Diffusion-weighted MRI showed acute infarction in the right corpus striatum suggesting transient occlusion of the M1 segment of the right middle cerebral artery; fluid attenuated inversion recovery MRI showed an established infarct in the same region with moderate background cerebral small vessel disease | CT and CT angiogram showed thrombotic occlusion of a proximal M2 branch of the right middle cerebral artery; a repeat CT at 24 hours showed a focus of parenchymal low density involving the right insular cortex in keeping with an evolving right middle cerebral artery territory infarct | Diffusion-weighted MRI showed acute infarction in the right thalamus, left pons, right occipital lobe and right cerebellar hemisphere. Time-of-flight images showed thrombotic material in the basilar artery and bilateral mild-to-moderate P2 segment stenosis |
| Chest | Chest X-ray: Bilateral pulmonary infiltrates CT pulmonary angiogram: Bilateral pulmonary embolism; semioclusive right middle lobe segmental and right lower lobe subsegmental, non-occlusive lower lobe subsegmental embolus | CT chest: Bilateral ground-glass change and consolidation CT pulmonary angiogram: No large pulmonary embolus within the main or segmental pulmonary arteries | Chest X-ray: Bilateral peripheral airspace opacities throughout both lungs, worse on the right | CT chest: Bilateral patchy subpleural airspace opacification in both lungs CT pulmonary angiogram: Pulmonary embolus in the left upper lobe segmental artery | Chest X-ray: few ill-defined patchy airspace opacifications seen peripherally in both lung fields mid-zones and lower zones, mild amount right-sided pleural effusion. CT pulmonary angiogram: No large pulmonary embolus within the main or segmental pulmonary arteries | Chest X-ray: Bilateral predominantly peripheral airspace opacities, most confluent at the mid-zones and the lung bases CT pulmonary angiogram: No large pulmonary embolus within the main or segmental pulmonary arteries |
| Other vascular imaging | Lower limb Doppler ultrasound: occlusive DVT in the left posterior tibial vein and the left peroneal vein | | | | | |

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supplementary figure S1B); he received high-intensity LMWH anticoagulation.

PATIENT 2

A 53-year-old woman, taking warfarin for valvular atrial fibrillation (AF), presented 24 days after COVID-19 symptom onset (cough, dyspnoea), with acute confusion, incoordination and drowsiness; CT brain confirmed acute large left cerebellar and right parieto-occipital infarcts (online supplementary figure S1 C, D). D-dimer was 7750 µg/L, and the International Normalised Ratio (INR) 3.6 at the time of stroke symptoms. Following external ventricular drainage for hydrocephalus she was given therapeutic LMWH anticoagulation. She died following cardiorespiratory deterioration due to COVID-19 pneumonia.

PATIENT 3

An 85-year-old man presented 10 days after COVID-19 symptom onset with dysarthria and right hemiparesis. He had AF, hypertension and ischaemic heart disease. CT brain showed left posterior cerebral artery occlusion and infarction (online supplementary figure S1 E, F). D-dimer was 16 100 µg/L. He was treated with apixaban for AF secondary prevention.

PATIENT 4

A 61-year-old man with hypertension, previous stroke and high body mass index presented with dysarthria and left hemiparesis. MRI brain showed an acute right striatal infarct (online supplementary figure S1 G, H). D-dimer was 27 190 µg/L. Two days following admission, he developed respiratory symptoms. RT-PCR confirmed SARS-CoV-2 infection and CT pulmonary angiogram an embolus. He was treated with therapeutic LMWH.

PATIENT 5

An 83-year-old man with a history of hypertension, diabetes, ischaemic heart disease, heavy smoking and alcohol consumption, presented with dysarthria and left hemiparesis 15 days after COVID-19 symptom onset. CT angiogram showed thrombotic occlusion of a proximal M2 branch of the right middle cerebral artery (online supplementary figure S2 A); the following day an infarct was shown in the right insula (online supplementary figure S2B). D-dimer was 19 450 µg/L. He was treated with intravenous thrombolysis.

Table 1 Continued

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|--|-----------|-----------|-----------|-----------|-----------|
| *Patient taking warfarin. DVT, Deep Vein Thrombosis; EGFR, Estimated Glomerular Filtration Rate; GCS, Glasgow Coma Score; ICU, intensive care unit. | | | | | |

PATIENT 6

A man in his 70s presented, 8 days after COVID-19 symptom onset, with dysphasia and right hemiparesis. MRI brain showed a thrombus in the basilar artery, bilateral P2 segment stenosis and multiple acute infarcts (right thalamus, left pons, right occipital lobe and right cerebellar hemisphere) (online supplementary figure S2 C, D, E, F). He received intravenous thrombolysis, after which D-dimer was 1080 µg/L.

DISCUSSION

SARS-CoV-2 infection is linked to a prothrombotic state causing venous and arterial thromboembolism and elevated D-dimer levels.² Severe COVID-19 is associated with proinflammatory cytokines which induce endothelial and mononuclear cell activation with expression of tissue factor leading to coagulation activation and thrombin generation. Circulation of free thrombin, uncontrolled by natural anticoagulants, can activate platelets and lead to thrombosis.² Although ischaemic stroke has been recognised as a complication of COVID-19 (usually with severe disease),³ the mechanisms and phenotype are not yet understood. Our observations suggest that acute ischaemic stroke accompanying Covid-19 infection may have distinct characteristics, with implications for diagnosis and treatment. All patients had large-vessel occlusion; in three these were in multiple territories. In two patients (1 and 2) one recurrent stroke and one initial ischaemic stroke, respectively, occurred despite therapeutic anticoagulation. Two patients had concurrent venous thromboembolism. Five patients had very high D-dimer levels (>7000 µg/L), substantially higher than the median level reported in COVID-19 (900 µg/L);³ the D-dimer for patient 6 was 1080 µg/L after intravenous thrombolysis. In five of six patients, ischaemic stroke occurred 8–24 days after Covid-19 symptom onset, and in one patient during the presymptomatic phase, suggesting that COVID-19 associated ischaemic stroke is usually delayed, but can occur both early and later in the course of the disease.

It has been suggested that COVID-19 might stimulate the production of anti-phospholipid antibodies (aPL)⁴ as a mechanism of ischaemic stroke, although

postinfection aPL are usually transient and unassociated with thrombosis. Five of six patients had a positive lupus anticoagulant, one with medium-titre IgM anticardiolipin and low-titre IgG and IgM anti-β₂-glycoprotein-1 antibodies. Screening for aPL might be reasonable in patients with COVID-19 associated ischaemic stroke, although their pathogenic relevance remains uncertain. All patients had elevated ferritin and lactate dehydrogenase levels, both of which have been reported in severe COVID-19.¹

Our data cannot confirm a causal relationship between SARS-CoV-2 and ischaemic stroke, since competing vascular risk factors and mechanisms were present in most patients (table 1); four of six had hypertension, and two had AF. It is also possible that the effects of social distancing measures and anxiety about attending hospital might have influenced the spectrum of ischaemic stroke mechanisms in patients seen at our hospital.

Nevertheless, our findings suggest that ischaemic stroke linked to Covid-19 infection can occur in the context of a systemic highly prothrombotic state, supporting recommendations for immediate prophylactic anticoagulation with LMWH.⁵ Early therapeutic anticoagulation with LMWH could also be beneficial to reduce thromboembolism in patients with COVID-19-associated ischaemic stroke but must be balanced against the risk of intracranial haemorrhage, including haemorrhagic transformation of the acute infarct; clinical trials are warranted to determine the safety and efficacy of this approach.

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