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. 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%). 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 April 1st and 16th 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 (≥1000μg/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 infarction with petechial haemorrhage (online supplementary figure S1A). D-dimer was >80000 μg/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 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 1600 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 27190 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 19450 μg/L. He was treated with intravenous thrombolysis.

**PATIENT 6**
A 73-year-old man 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. 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. Although ischaemic stroke has been recognised as a complication of COVID-19 (usually with severe disease), 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); 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) as a mechanism of ischaemic stroke, although postinfection aPL are usually transient and unassociated with thrombosis. Five
Table 1 Demographic, clinical, radiological and laboratory findings

| Patient | Age, years | Sex | Medical history | Symptoms at COVID-19 disease onset | Initial treatment | Days from COVID-19 symptom onset to ICU admission | Clinical symptoms of ischaemic stroke | ICU admission and disease severity | Laboratory findings on the day of first or only ischaemic stroke event | Imaging features |
|---------|------------|-----|----------------|-----------------------------------|------------------|-------------------------------------------------|-----------------------------------|--------------------------------|-----------------------------------------------|----------------|
| 1       | 64         | Male| Nil            | Shortness of breath, fever, cough | Antibiotics, oxygen therapy | 15                 | Word finding difficulties, bilateral incoordination, right-sided hemianopia | Did not go to ICU | Haemoglobin (g/L) 119 | MRI including diffusion-weighted and susceptibility-weighted imaging showed acute left ventricular artery thrombus and acute left posterior inferior cerebellar artery territory infarction with posterior hemorrhagic transformation. 7 days later, diffusion-weighted MRI showed bilateral acute posterior cerebral artery territory infarct despite therapeutic anticoagulation. | |
| 2       | 53         | Female|              | Shortness of breath, fever, cough | Supportive        | 24                 | Acute confusion, incoordination, reduced consciousness (GCS 13/15) | Did not go to ICU | White cell count (mm³) 6750 | Glucose 4.96 | |
| 3       | 85         | Male| Hypertension, diabetes, mitral valve replacement, atrial fibrillation, heart failure with a permanent pacemaker | Malaise, dry cough, shortness of breath, fever | Supportive        | 10                | Dysautonia, right facial droop and right-sided weakness | Did not go to ICU | Neutrophils 5810 | CT and CT angiogram showed an established infarct in the same region with moderate background cerebral small vessel disease | |
| 4       | 61         | Male| Hypertension, hypertensive encephalopathy, atrial fibrillation, ischemic heart disease, prostate cancer (Gleason Score 4-3) | Fever, cough, shortness of breath, tachypnoea | Antibiotics       | 15                | Dysautonia, left facial droop and left-sided weaknesses | Did not go to ICU | Lymphocytes 4701 | CT and CT angiogram showed an established infarct in the same region with moderate background cerebral small vessel disease | |
| 5       | 83         | Male| Hypertension, stroke, chronic leg ulcers | Fever, cough, shortness of breath, tachypnoea | Antibiotics, oxygen therapy | 15                | Dysautonia, left facial droop and left-sided weakness and left-sided sensory inattention | Did not go to ICU | Monocytes 370 | CT and CT angiogram showed an established infarct in the same region with moderate background cerebral small vessel disease | |
| 6       | 73         | Male| Gastric carcinoma (resected), benign essential tremor | Fever, cough, shortness of breath, fatigue | Antibiotics, oxygen therapy | 8                 | Aphasia, right facial droop and right-sided weakness | Did not go to ICU | Platelet count (mm³) 305 000 | CT and CT angiogram showed an established infarct in the same region with moderate background cerebral small vessel disease | |

*Patient taking warfarin.
DVT, Deep Vein Thrombosis; EGFR, Estimated Glomerular Filtration Rate; GCS, Glasgow Coma Score; ICU, intensive care unit.
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.

Rahma Beyrouti,1 Matthew E Adams,2 Laura Benjamin,3,4 Hannah Cohen,3 Simon F Farmer,1 Yee Yen Goh,3 Fiona Humphries,1 Hans Rolf Jäger,2,7 Nicholas A Losseff,1,4 Richard J Perry,1,4 Sachit Shah,2 Robert J Simister,1,4 David Turner,1 Arvind Chandratheva,1,4 David J Werring ◊1,4
1Comprehensive Stroke Service, University College London Hospitals NHS Foundation Trust, London, UK
2Lysholm Department of Neuroradiology, University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, London, UK
3Brain Infections Group, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
4Stroke Research Centre, UCL Queen Square Institute of Neurology, London, UK
5Haemostasis Research Unit, Department of Haematology, University College London, London, UK
6Department of Neurology, University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, London, UK
7Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, London, UK
8Cleveland Clinic, Grosvenor Place, London SW1 X7HY, United Kingdom

Correspondence to Professor David J Werring, Stroke Research Centre, UCL Queen Square Institute of Neurology, London WC1B 5EH, UK; d.werring@ucl.ac.uk

Correction notice This paper has been corrected since it was published Online First. The following standard funding statement has been added, along with minor formatting changes. “This work was undertaken at UCLH/UCL which receives a proportion of funding from the Department of Health’s National Institute for Health Research (NIHR) Biomedical Research Centre funding scheme.”

Contributors DJW and AC had the idea for the paper. RB prepared the first draft with DJW and AC. DJW prepared the draft figures. MEA and SS assisted with imaging interpretation and critically reviewed the manuscript for intellectual content. AC, DJW, RB, HC, SFF, YYG, FH, RJH, DT, NAL and RJP were involved in the clinical care of the patients and critically reviewed the manuscript for intellectual content. HJU assisted with imaging interpretation and preparation of the figures, and critically reviewed the manuscript for intellectual content.

Funding This work was undertaken at UCLH/UCL which receives a proportion of funding from the Department of Health’s National Institute for Health Research (NIHR) Biomedical Research Centre funding scheme.

Competing interests DJW has received personal fees from Bayer, Alnylam and Portola, outside the submitted work

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2020-323586).

AC and DJW contributed equally.

To cite Beyrouti R, Adams ME, Benjamin L, et al. J Neurol Neurosurg Psychiatry 2020;91:889–891. Received 24 April 2020 Accepted 27 April 2020 Published Online First 30 April 2020

ORCID iD David J Werring http://orcid.org/0000-0003-2074-1861

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J Neurol Neurosurg Psychiatry August 2020 Vol 91 No 8 891