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 (≥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 >80 000 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 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.

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-2infection 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 antiphospholipid antibodies (aPL)[4] 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 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 (/mm^3)						
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 (µmol/L)	11	29↑	17	13	11	10
Lactate dehydrogenase (U/L)	654↑	664↑	461↑	444↑	353↑	439↑
Creatinine (µmol/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
Fibrinogen (g/L)	9.5 ↑	7.03	5.3↑	4.63↑	4.96↑	–
D-dimer (µg/L)	>80 000 ↑	7750↑	16 100↑	27 190↑	19 450↑	1080↑
Serum ferritin (µg/L)	4927 ↑	1853↑	1027↑	1167↑		655↑
High-sensitivity C reactive protein (mg/L)	305.4 ↑	150.1↑	161.2↑	12.8	27.7↑	179.9↑
Antiphospholipid antibodies: Anticardiolipin (aCL) Anti-β2-glycoprotein-1 (aβ2GPI)	Medium titre IgM aCL IgG aCL negative Low titre IgG and IgM aβ2GP1	IgG and IgM aCL and aβ2GP1 negative	IgG and IgM aCL and aβ2GP1 negative	IgG and IgM aCL and aβ2GP1 negative	IgG and IgM aCL and aβ2GP1 negative	IgG and IgM aCL and aβ2GP1 negative
Lupus anticoagulant	Positive	Positive	Negative	Positive	Positive	Positive
Imaging features						
Brain (online supplementary figures S1 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; semiocclusive 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					

*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,[5] Simon F Farmer,[6] Yee Yen Goh,[6] Fiona Humphries,[1] Hans Rolf Jäger,[2,7] Nicholas A Losseff,[1,8] 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]

[1]Comprehensive Stroke Service, University College London Hospitals NHS Foundation Trust, London, UK
[2]Lysholm Department of Neuroradiology, University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, London, UK
[3]Brain Infections Group, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
[4]Stroke Research Centre, UCL Queen Square Institute of Neurology, London, UK
[5]Hemostasis Research Unit, Department of Hematology, University College London, London, UK
[6]Department of Neurology, University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, London, UK
[7]Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, London, UK
[8]Cleveland 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 Centres 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, RJS, DT, NAL and RJP were involved in the clinical care of the patients and critically reviewed the manuscript for intellectual content. HRJ 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 Centres 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.

OPEN ACCESS

► 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.

Check for updates

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

Linked

► http://dx.doi.org/10.1136/jnnp-2020-323667

J Neurol Neurosurg Psychiatry 2020;**91**:889–891. doi:10.1136/jnnp-2020-323586

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

REFERENCES

1 Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* 2020;395:507–13.
2 Tang N, Li D, Wang X, *et al*. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7.
3 Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020 (published Online First: 2020/04/11).
4 Zhang Y, Xiao M, Zhang S, *et al*. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020 (published Online First: 2020/04/09).
5 Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of Thrombosis and Haemostasis*;n/a(n/a).