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 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 77 500 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 160 100 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 showed 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-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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Medical history</th>
<th>Symptoms at COVID-19 disease onset</th>
<th>Initial treatment</th>
<th>Days from COVID-19 symptom onset to ischaemic stroke symptom onset</th>
<th>Clinical symptoms of ischaemic stroke</th>
<th>ICU admission and disease severity</th>
<th>Laboratory findings on the day of first or only ischaemic stroke event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>Male</td>
<td>Nil</td>
<td>Cough, shortness of breath, fever, myalgia, loss of appetite</td>
<td>Anticoagulants, oxygen therapy</td>
<td>15 days from COVID-19 symptom onset to ICU admission</td>
<td>Word finding difficulties, bilateral incoordination, right homonymous hemianopia</td>
<td>Severe</td>
<td>Haemoglobin (g/L) 119↑</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Critical</td>
<td>Neutrophils 470↑</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>Male</td>
<td>Hypertension, diabetes, mitral valve replacement, atrial fibrillation, heart failure with a permanent pacemaker</td>
<td>Malaise, dry cough, shortness of breath, fever</td>
<td>Supportive</td>
<td>24 days from COVID-19 symptom onset to ICU admission</td>
<td>Acute confusion, incoordination, reduced consciousness (GCS 13/15)</td>
<td>Moderate to severe</td>
<td>Lymphocytes 9.5↑</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Male</td>
<td>Hypertension, hypercholesterolaemia, atrial fibrillation, ischaemic heart disease, prostate cancer (Gleason Score 4-3)</td>
<td>Fever, cough, shortness of breath, tachypnoea</td>
<td>Supportive</td>
<td>10 days from COVID-19 symptom onset to ICU admission</td>
<td>Dysharmony, right facial droop and right-sided weakness</td>
<td>Moderate</td>
<td>Albumin (g/L) 28↓</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>Male</td>
<td>Hypertension, stroke, chronic leg ulcers</td>
<td>Fever, cough, shortness of breath, fatigue</td>
<td>Antibiotics</td>
<td>2-3 days from COVID-19 symptom onset by 2 days</td>
<td>Dysharmony, left facial droop and left-sided weakness</td>
<td>Severe</td>
<td>Lactate dehydrogenase (U/L) 137↑</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>Male</td>
<td>Gastric carcinoma (resected), benign essential tremor</td>
<td>Shortness of breath, tachypnoea</td>
<td>Antibiotics, oxygen therapy</td>
<td>15 days from COVID-19 symptom onset to ICU admission</td>
<td>Aphasias, right facial droop and right-sided weakness</td>
<td>Severe</td>
<td>Creatinine (μmol/L) 57↑</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Male</td>
<td>Nil</td>
<td></td>
<td>Antibiotics, oxygen therapy</td>
<td>8 days from COVID-19 symptom onset to ICU admission</td>
<td>Acute confusion, incoordination, reduced consciousness (GCS 13/15)</td>
<td>Severe</td>
<td>C reactive protein (mg/L) 304.5↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Nil</td>
<td></td>
<td>Antibiotics, oxygen therapy</td>
<td></td>
<td></td>
<td>Critical</td>
<td>Lymphocytes 5.8↑</td>
</tr>
</tbody>
</table>

**Table 1** Demographic, clinical, radiological and laboratory findings

- **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
- **Symptoms at COVID-19 disease onset**: Cough, shortness of breath, fever, myalgia, loss of appetite
- **Initial treatment**: Anticoagulants, oxygen therapy
- **Days from COVID-19 symptom onset to ischaemic stroke symptom onset**: 15, 24, 10, 2-3 days, 10, 8
- **Clinical symptoms of ischaemic stroke**: Word finding difficulties, bilateral incoordination, right homonymous hemianopia
- **ICU admission and 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↑, White cell count (mm$^3$) 6750↑, Neutrophils 5810↑, Lymphocytes 470↑, Monocytes 370, Platelet count (mm$^3$) 305 000, Albumin (g/L) 28↓, Alkaline phosphatase (U/L) 137↑, Bilirubin (μmol/L) 29↑, Lactate dehydrogenase (U/L) 654↑, Creatinine (μmol/L) 57↑, EGRF (ml/min/1.73 m$^2$) >90, High-sensitivity cardiac troponin I (pg/ml) 9↑, Prothrombin time (s) 12.5↑, Serum ferritin (μg/L) 4927↑, High-sensitivity C reactive protein (mg/L) 304.5↑, Antiphospholipid antibodies: Anticardiolipin (aCL) Medium titre IgM aCL negative, Low titre IgM and IgG aCL negative, Lupus anticoagulant Positive, Non-contrasted CT showed acute right hemispheric stroke and left carotid infarct with mass effect and hydrocephalus, despite therapeutic anticoagulation

**Brain**
- **MRI including diffusion-weighted and susceptibility-weighted imaging showed acute left ventricular 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 cerebellar artery territory infarcts despite therapeutic anticoagulation
- **Diffusion-weighted MRI showed acute infarction in the right corpus striatum suggesting transient occlusion of the M2 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 inferior 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**
- **CT chest**: Bilateral ground-glass change and consolidation
- **CT pulmonary angiogram**: No large pulmonary emboli within the main or segmental pulmonary arteries
- **Diffusion-weighted MRI showed acute infarction in the right middle cerebral artery; a repeat CT at 24 hours showed a focus of parenchymal low density involving the right inferior cortex in keeping with an evolving right middle cerebral artery territory infarct
- **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 inferior 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**

**Other vascular imaging**
- **Lower limb Doppler ultrasound**: Occlusive DVT in the left posterior tibial vein and the left peroneal vein

**Notes**
- *Patient taking warfarin.
- DVT, Deep Vein Thrombosis; EGRF, 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. 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 Hannah Cohen,3 Simon F Farmer,3 Yee Yen Goh,4 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 Chandrathave,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, Grosvener 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 DIW and AC had the idea for the paper; RB prepared the first draft with DIW and AC. DIW prepared the draft figures. MEA and SS assisted with imaging interpretation and critically reviewed the manuscript for intellectual content. AC, DIW, RB, HC, SFF, YGY, FH, RJS, DT, NAL and RJP were involved in the clinical care of the patients and critically reviewed the manuscript for intellectual content. HJL 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 DIW 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 This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

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

AC and DIW contributed equally.


Received 24 April 2020
Accepted 27 April 2020
Published Online First 30 April 2020

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


doi:10.1136/jnnp-2020-323586

ORCID iD

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

REFERENCES


OPEN ACCESS

J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp-2020-323586 on 30 April 2020. Downloaded from http://jnnp.bmj.com/ on November 15, 2022 by guest. Protected by