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 pulmo-

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 infarc-

PATIENT 4
A 61-year-old man with hypertension, previous stroke and high body mass index presented with dysartrhia and left hemiparesis. MRI brain showed an acute right striatal infarct (online supple-

PATIENT 5
An 83-year-old man with a history of hypertension, diabetes, ischaemic heart disease, heavy smoking and alcohol consumption, presented with dysars-

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 cyto-

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

19450 µg/L. He was treated with intravenous thrombolysis.

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 cyto-

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>Demographic characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64</td>
<td>53</td>
<td>85</td>
<td>61</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Medical history</td>
<td>Nil</td>
<td>Hypertension, diabetes, mitral valve replacement, atrial fibrillation, heart failure with a permanent pacemaker</td>
<td>Hypertension, hypercholesterolaemia, atrial fibrillation, ischaemic heart disease, prostate cancer (Gleason Score 4-5)</td>
<td>Hypertension, stroke, chronic leg ulcers</td>
<td>Hypertension, diabetes, ischaemic heart disease, smoking and alcohol consumption</td>
<td>Gastric carcinoma (resected), benign essential tremor</td>
</tr>
<tr>
<td>Symptoms at COVID-19 disease onset</td>
<td>Cough, shortness of breath, fever, myalgia, loss of appetite</td>
<td>Malaise, dry cough, shortness of breath, fever</td>
<td>Cough</td>
<td>Fever, cough, shortness of breath, tachypnoea</td>
<td>Fever, cough, shortness of breath, fatigue</td>
<td>Shortness of breath, tachypnoea</td>
</tr>
<tr>
<td>Initial treatment</td>
<td>Antibiotics, oxygen therapy</td>
<td>Supportive</td>
<td>Supportive</td>
<td>Antibiotics</td>
<td>Antibiotics, oxygen therapy</td>
<td>Antibiotics, oxygen therapy</td>
</tr>
<tr>
<td>Days from COVID-19 symptom onset to ICU admission</td>
<td>15</td>
<td>24</td>
<td>10</td>
<td>–2 (stroke preceded COVID-19 symptoms by 2 days)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Clinical symptoms of ischaemic stroke</td>
<td>Word finding difficulties, bilateral incoordination, right homonymous hemianopia</td>
<td>Acute confusion, incoordination, reduced consciousness (GCS 13/15)</td>
<td>Dysarthria, right facial droop and right-sided weakness</td>
<td>Dysarthria, left facial droop and left-sided weakness</td>
<td>Dysarthria, left facial droop and right-sided weakness</td>
<td>Aphasia, right facial droop and right-sided weakness</td>
</tr>
</tbody>
</table>

**ICU admission and disease severity**

<table>
<thead>
<tr>
<th>Days from COVID-19 symptom onset to ICU admission</th>
<th>Did not go to ICU</th>
<th>Did not go to ICU</th>
<th>Did not go to ICU</th>
<th>Did not go to ICU</th>
<th>Did not go to ICU</th>
<th>Did not go to ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 disease severity</td>
<td>Severe</td>
<td>Critical</td>
<td>Moderate to severe</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Laboratory findings on the day of first or only ischaemic stroke event**

<table>
<thead>
<tr>
<th>Haemoglobin (g/L)</th>
<th>119</th>
<th>94</th>
<th>128</th>
<th>126</th>
<th>121</th>
<th>142</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (mm³)</td>
<td>6750</td>
<td>23 050</td>
<td>5080</td>
<td>8970</td>
<td>11 030</td>
<td>7300</td>
</tr>
<tr>
<td>Differential count (mm³)</td>
<td>5810</td>
<td>19 200</td>
<td>4440</td>
<td>6390</td>
<td>8330</td>
<td>5800</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>470</td>
<td>2070</td>
<td>402</td>
<td>1310</td>
<td>1630</td>
<td>1250</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>370</td>
<td>1660</td>
<td>180</td>
<td>900</td>
<td>830</td>
<td>470</td>
</tr>
<tr>
<td>Monocytes</td>
<td>305 000</td>
<td>254 000</td>
<td>173 000</td>
<td>408 000</td>
<td>197 000</td>
<td>403 000</td>
</tr>
<tr>
<td>Platelet count (mm³)</td>
<td>28</td>
<td>28</td>
<td>33</td>
<td>31</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Eosinophils (±)</td>
<td>137</td>
<td>27</td>
<td>32</td>
<td>24</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>Basophils (±)</td>
<td>11</td>
<td>29</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>644</td>
<td>664</td>
<td>461</td>
<td>444</td>
<td>353</td>
<td>439</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>57</td>
<td>75</td>
<td>77</td>
<td>107</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>EGRF (min/ml/7.3 m²)</td>
<td>&gt;90</td>
<td>74</td>
<td>87</td>
<td>64</td>
<td>&gt;90</td>
<td>64</td>
</tr>
<tr>
<td>High-sensitivity cardiac troponin I (pg/ml)</td>
<td>9</td>
<td>42</td>
<td>32</td>
<td>30</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>12.5</td>
<td>34.4</td>
<td>11.3</td>
<td>10.9</td>
<td>11.7</td>
<td>12.3</td>
</tr>
<tr>
<td>International normalised ratio (INR)</td>
<td>1.14</td>
<td>3.6</td>
<td>1.03</td>
<td>0.99</td>
<td>1.07</td>
<td>1.13</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT) (s)</td>
<td>35</td>
<td>41</td>
<td>33</td>
<td>24</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>APPR ratio</td>
<td>1.1</td>
<td>1.3</td>
<td>1</td>
<td>0.8</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>9.5</td>
<td>7.0</td>
<td>5.3</td>
<td>4.6</td>
<td>4.9</td>
<td>–</td>
</tr>
<tr>
<td>D-dimer (µg/L)</td>
<td>&gt;80000</td>
<td>7750</td>
<td>16000</td>
<td>27 190</td>
<td>19 450</td>
<td>1080</td>
</tr>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>4927</td>
<td>1853</td>
<td>1027</td>
<td>1167</td>
<td>837</td>
<td>655</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>30 32</td>
<td>31 0.8</td>
<td>1.07</td>
<td>1.63</td>
<td>27</td>
<td>17.7</td>
</tr>
<tr>
<td>Antiphospholipid antibodies: Anti-cardiolipin (aCL)</td>
<td>150.4</td>
<td>Medium titre IgM aCL, IgG and IgM aCL and a2B2GPI negative</td>
<td>IgG and IgM aCL and a2B2GPI negative</td>
<td>IgG and IgM aCL and a2B2GPI negative</td>
<td>IgG and IgM aCL and a2B2GPI negative</td>
<td>IgG and IgM aCL and a2B2GPI negative</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Imaging features**

| Brain (online supplementary figures S1 and S2) | MRI including diffusion-weighted and susceptibility-weighted imaging showed acute left ventricular artery thrombus and acute left posterior inferior cerebral artery territory infarction with periventricular haemorraghic transformation. 7 days later, diffusion-weighted MRI showed bilateral acute posterior cerebral artery territory infarction despite therapeutic anticoagulation | Non-contract CT showed acute right parietal cortical and left cerebellar infarct with mass effect and hydrocephalus, despite therapeutic anticoagulation | Non-contract CT showed hyperdense 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 cortex stratum 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 mid-to-moderate P2 segment stenosis |
| Chest | Chest X-ray: Bilateral pulmonary infiltrates; CT pulmonary angiogram: Bilateral pulmonary embolism; semicircular right middle lobe segmental and right lower lobe subsegmental, non-occlusive lower lobe subsegmental embolus | Chest X-ray: 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: No large pulmonary embolus within the main or segmental pulmonary arteries | 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 antiphospholipid 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.3 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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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, YYG, FH, RJS, 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 Centres funding scheme.

Competing interests DIW has received personal fees from Bayer, Ahylam 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 DIW contributed equally.


Received 24 April 2020

Accepted 27 April 2020

Published Online First 30 April 2020

http://dx.doi.org/10.1136/jnnp-2020-323586

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REFERENCES


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