



Bilateral lower limb weakness: a cerebrovascular consequence of covid-19 or a complication associated with it?

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Dear Editor,

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel virus first identified in China, that results in coronavirus disease 2019 (Covid-19). Patients with Covid-19 often present with a prodrome of symptoms including fever, cough and dyspnoea following exposure to SARS-CoV-2 [1]. In some individuals the dyspnoea may rapidly progress, culminating in severe hypoxia necessitating mechanical ventilation. To-date, Covid-19 is managed supportively as there are no proven treatments. Infection with SARS-CoV-2 is associated with a number of complications; typically renal insufficiency, venous and arterial thromboembolic, and myocardial complications. In this paper, we describe two patients admitted with confirmed (via reverse transcriptase-polymerase chain reaction (RT-PCR) testing) severe Covid-19 needing mechanical ventilation and renal support during their intensive care admission, who on stepping down were noted to have lower limb weakness.

The first patient was a 75-year old Caucasian never smoker, retired IT recruitment manager with a medical history of ischaemic heart disease and bypass surgery in 2001, chronic kidney disease, hypertension and dyslipidaemia. On 25th of March, he was admitted to a district general hospital

with a week's history of worsening dyspnoea. At admission, he was in respiratory failure and acute (on chronic) kidney injury (AKI), and within a few hours required mechanical ventilation and initiated on intravenous (IV) antibiotics for a left lower zone consolidation (Fig. 1a; Table 1). Due to ICU bed pressures, he was moved, 2 days later, to our hospital (a tertiary centre). He made a good respiratory recovery and was weaned of its support and oxygen over the next 48 h though did have 36 h of continuous veno-venous haemofiltration (CVVHF). Additionally, with high D-dimer levels at admission he was maintained on therapeutic IV unfractionated heparin; a CTPA conducted showed multiple segmental and sub-segmental filling defects, with widespread ground-glass opacities (GGOs) and areas of consolidation/atelectasis (Fig. 1b). Subsequently, he was changed over to a new oral anti-coagulant (NOAC). Over the next 7 days, despite routine physiotherapy, the patient failed to convalesce with weakness in the lower limbs. Neurological examination of the lower limbs revealed an increased tone and reduced power bilaterally though more pronounced on the left. There was no loss of pulses or any sensory findings in the lower limbs and the Babinski sign was negative; coordination and gait were challenging to assess as the patient needed hoisting to stand. A CT scan of the head showed no

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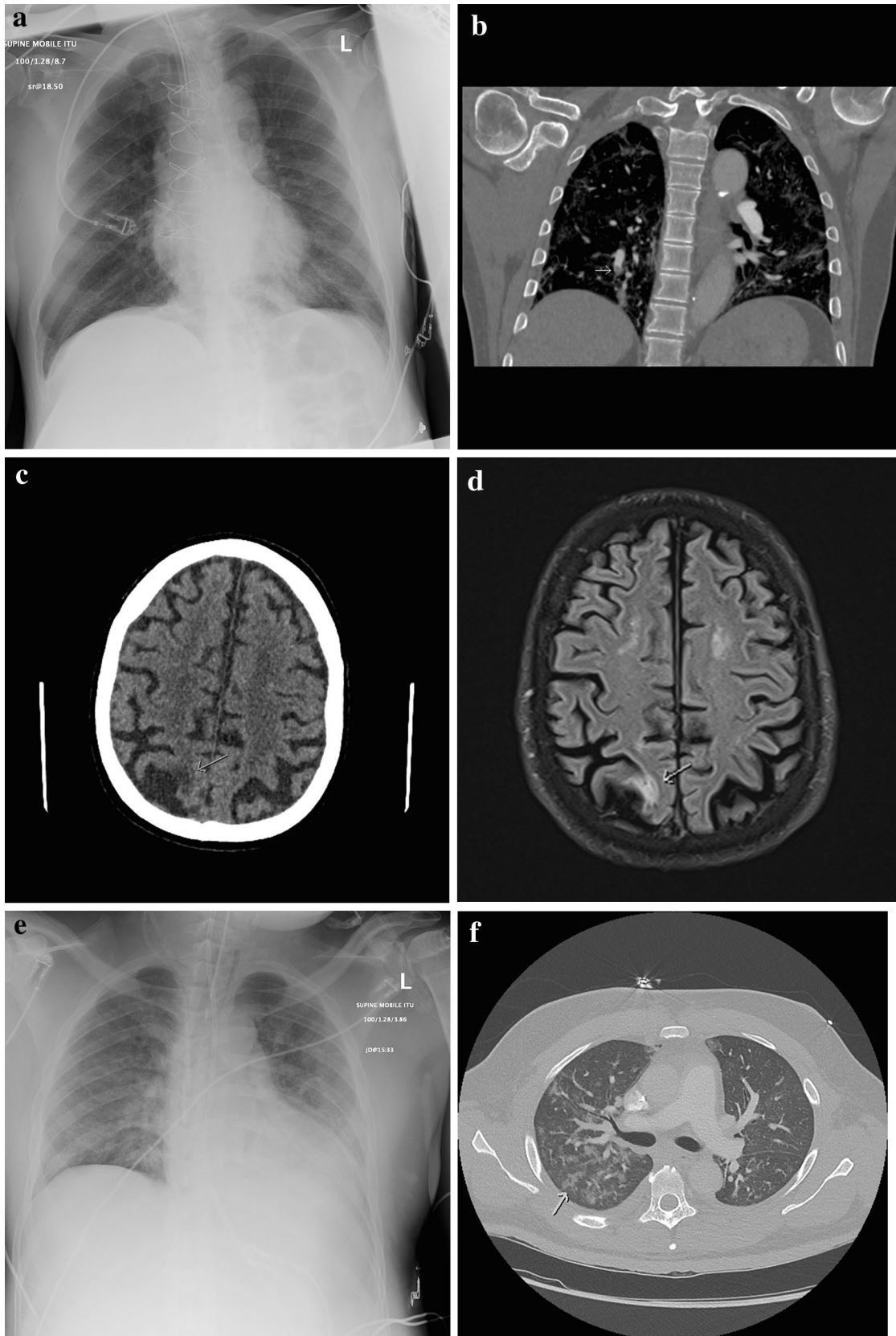
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◀ **Fig. 1 a** Chest radiograph depicting developing consolidation in the left lower lobe in a patient who had undergone the previous sternotomy. **b** Coronal computed tomographic (CT) images taken from a CT pulmonary angiogram study reveal a subsegmental right lower lobe filling defect (arrow) consistent with pulmonary embolus. **c** Axial CT showing right parieto-occipital changes (arrow). **d** Magnetic Resonance (MR) Images reveal high signal on the inversion recovery MR images suggesting sub-acute ischaemic changes. **e** Chest radiograph of an intubated patient which reveals collapse/con-

solidation in the left lower lobe and multifocal alveolar consolidation elsewhere in both lungs. **f** Axial CT image reveals serpiginous and peribronchovascular ground glass opacity and consolidation (arrow) consistent with the patient's known viral illness. **g** Coronal CT reconstruction from a CT pulmonary angiogram reveals a posterior right lower lobe filling defect in a segmental vessel consistent with pulmonary embolus (arrow). **h** Axial MR inversion recovery sequence image reveals multiple periventricular foci of high signal (arrows) consistent with sub-acute ischaemic changes

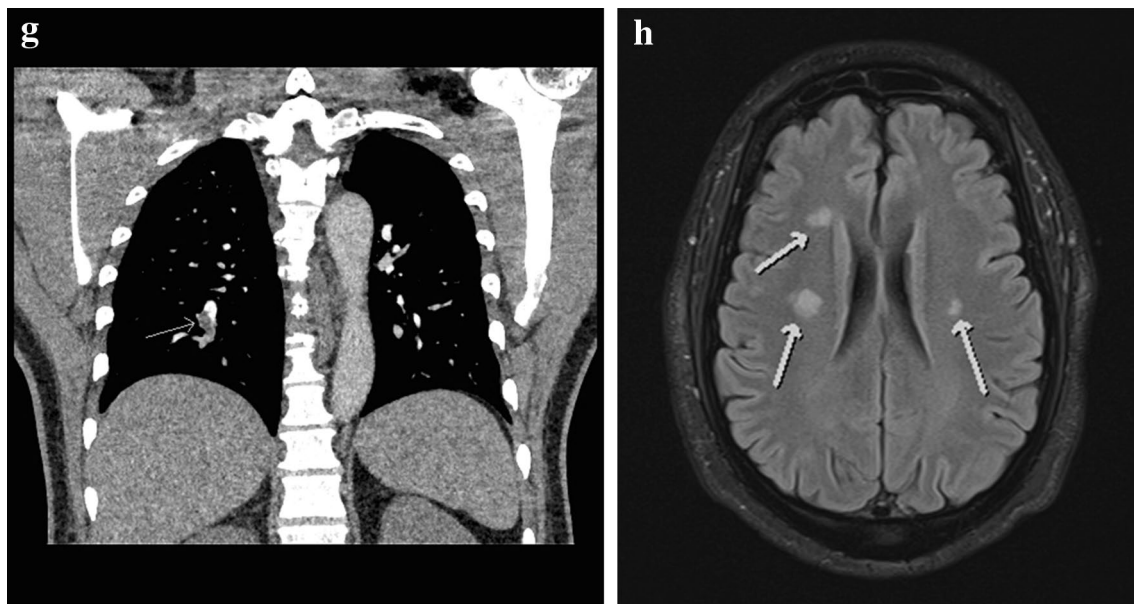


Fig. 1 (continued)

acute intracranial abnormality (Fig. 1c). Persistent bilateral lower limb weakness and stiffness prompted a magnetic resonance imaging (MRI) scan of the head; this showed small vessel disease and infarcts in the parietal and occipital lobes, and in the midbrain and basal ganglia (Fig. 1d). The patient was subsequently moved to a neuro-rehabilitation centre on the 27th of April for ongoing management/ convalescence.

The second patient was a 49-year old never smoker Afro-Caribbean security guard with non-insulin dependent diabetes mellitus and hypertension. On the 29th of March, he was admitted with a 5-day history of cough, pyrexia and dyspnoea. His CXR showed left-sided patchy consolidation for which he started on IV antibiotics and unfractionated heparin for elevated D-dimers (Fig. 1e; Table 1), and was initiated on CPAP therapy due to being hypoxic, though continued to deteriorate and was later intubated. He was transferred to our ICU due to bed pressures on the 31st of March where he was initiated on CVVHF for worsening AKI. From a respiratory perspective, he improved and was extubated on the 6th of April, and weaned of supplementary oxygen though still needed renal support intermittently. A renal ultrasound scan showed no

abnormalities and a CTPA demonstrated a segmental pulmonary embolus, bilateral scattered air space shadowing and GGOs and small areas of consolidation (Fig. 1f and Fig. 1g). An echocardiogram on the 21st of April showed good biventricular function and no valvular or structural abnormalities. Despite routine physiotherapy, he had persistent bilateral lower limb weakness. Lower limb evaluation showed reduced power bilaterally (left > right) with difficulty in mobilising and coordination though the reflexes and sensation as well as peripheral pulses were intact. No significant upper limb neurological examination abnormalities were identified. An MRI scan showed an abnormal signal in the deep white matter bilaterally, likely to represent subcortical watershed infarcts (Fig. 1h). Akin to the first patient, with the increased rehabilitation requirements he was transferred to neuro-rehabilitation unit on the 27th of April.

Both our patients had prolonged hospital stays with early improvements in their respiratory symptoms despite warranting mechanical ventilation, though developed unexpected new neurological issues. Additionally, they both required CVVHF for acute kidney injury, developed venous

Table 1 Blood measurements and Covid-19 RT-PCR swabs over the course of the admission spaced out at approximately 5 days apart in Patients 1 and 2

Patient 1									
Blood Test	Dates when blood tests conducted								Normal Range
	27/03/20 (Admission)	28/03/20	01/04/20	06/04/20	11/04/20	16/04/20	21/04/20	27/04/20 (Discharge)	
WCC	15.6	13.0	6.5	8.1	13.4	7.5	8.2	5.4	4.4–10.1 ($\times 10^9/L$)
Neutrophils	14.2	11.7	5.1	6.6	11.4	5.6	6.2	3.7	2.1–6.7 ($\times 10^9/L$)
Lymphocytes	0.3	0.4	0.6	0.6	0.9	0.6	0.9	0.8	1.3–3.7 ($\times 10^9/L$)
Urea	23.3	23.7	28.0	20.6	24.8	11.7	9.3	8.8	2.5–7.8 (mmol/L)
Creatinine	163	163	147	150	151	63	89	107	60–120 ($\mu\text{mol/L}$)
CRP	155	165	43	20	88	54	17	4	0–10 (mg/L)
D-dimer	–	8974	6264	–	4005	4597	3006	1034	0–240 (ng/ml)
Ferritin	–	506	323	253	296	307	311	303	32–284 ($\mu\text{g/L}$)
LDH	–	–	579	628	703	433	802	–	266–500 (IU/L)
hs Troponin	379.9	121	7.8	6.8	–	8.6	9.7	–	< 19.8 (ng/L)
Covid-19 RT-PCR swab	+ve (25/03/20)					-ve (16/04/20)	-ve (19/04/20)		–

Patient 2									
Blood Test	Dates when blood tests conducted							Normal Range	
	31/03/20 (Admission)	05/04/20	10/04/20	14/04/20	20/04/20	25/04/20	27/04/20 (Discharge)		
WCC	17.0	29.6	18.7	10.2	6.7	6.5	7.2	4.4–10.1 ($\times 10^9/L$)	
Neutrophils	12.9	24.6	14.0	7.4	3.5	4.2	4.0	2.1–6.7 ($\times 10^9/L$)	
Lymphocytes	2.4	1.8	2.6	1.3	1.7	1.2	1.7	1.3–3.7 ($\times 10^9/L$)	
Urea	19.7	14.2	37.7	22.9	19.2	11.8	10.9	2.5–7.8 (mmol/L)	
Creatinine	669	309	745	612	509	264	225	60–120 ($\mu\text{mol/L}$)	
CRP	279	67	11	26	12	3	4	0–10 (mg/L)	
D-dimer	7204	2868	1751	727	811	17239	2236	0–240 (ng/ml)	
Ferritin	699	1848	762	454	240	235	493	32–284 ($\mu\text{g/L}$)	
LDH	1141	1122	719	555	491	346	–	266–500 (IU/L)	
hs Troponin	–	24.7	18.4	11.6	7.0	–	–	< 19.8 (ng/L)	
Covid-19 RT-PCR swab	+ve (29/03/20)			-ve (17/04/20)	-ve (20/03/20)				–

This was done as there trend of change in the relevant parameters are available for the readers. Blank spaces indicate the particular blood parameter was not requested on that day

WCC white cell count, CRP C-reactive protein, LDH lactate dehydrogenase, hs high sensitivity, mmol/L millimoles per litre, $\mu\text{mol/L}$ micromoles per litre, mg/L milligram per litre, ng/ml nanogram per millilitre, $\mu\text{g/L}$ microgram per litre, IU/L international units per litre, ng/L nanogram per litre, Covid-19 coronavirus disease 2019, RT-PCR reverse transcriptase-polymerase chain reaction

thromboemboli in spite of being on therapeutic anti-coagulation and increases in cardiac markers.

Covid-19 has been associated with a number of neurological manifestations ranging from acute cerebrovascular manifestations, impaired consciousness and skeletal muscle injury [2]. The neurological findings described in the two patients in this report may have occurred due to a number of possibilities. Coagulopathy is a frequent anomaly identified in Covid-19 patients; in fact, cases of venous thromboembolism have also been identified in individuals treated

with therapeutic doses of anti-coagulation [3]. This was the case in both patients discussed. The rates of arterial embolic events have been reported at 3.7% [4] and 5.7% [2] in recent observations. Although no clear mechanisms have been identified to explain these clinical manifestations it has been postulated that the thromboembolic disease may be due to hypoxia, diffuse intravascular coagulation, cardio-embolism from cardiac injury related to Covid-19 and exaggerated systemic inflammation [5].

Whilst we postulate that in both patients that the aetiology of the cerebrovascular accidents were due to embolic events associated with the elevated inflammatory state promoting high levels of prothrombotic blood markers generated by SARS-CoV-2, other explanations may also be postulated. These may include poor perfusion due to underlying atherosclerosis from hypertension and diabetes, in combination with the significant hypoxia from the ARDS; and acute cardiac injury during Covid-19. The latter may result in poor cardiac output and hence circulation resulting in cerebrovascular events. Moreover, other vascular aetiology such as rupture, occlusion, dissection or external compression in the abdomen or spine may be possibilities though there were good peripheral pulses and no loss of sensation hence making these possibilities less likely [6]. It may also be possible that in both our cases additional spinal pathology may have been present in addition to the central pathologies identified on imaging. These may include critical illness neuropathy and/or myopathy or a post-viral transverse myelitis. Appropriate imaging as well as supplementary investigations such as nerve conduction or electromyographic tests would have been helpful to exclude these differentials but due to the lack of other clinical pointers and also to minimise the risk of Covid-19 infection spread these were not conducted. Additionally, direct viral invasion via the ACE-2 receptors may result in localised intracranial damage [2]. Lastly, although less likely, the use of sedative and anaesthetic agents, and other transient haemodynamic events during the admission may culminate in the neurology noted.

A common finding in our patients was AKI necessitating the need for renal support; AKI can be life-threatening in critically ill patients [7]. Beta coronaviruses, including the SARS-CoV-2, may utilise ACE-2 receptors which are abundant in the kidneys, to infect renal tubular cells and perpetuate the inflammatory response, resulting in the incidence and length of AKI. Clinicians need to be vigilant in AKI identification, especially on the background of other co-morbidities, and initiate early appropriate renal support to prevent complications.

SARS-CoV-2 has been reported to involve multiple organ systems in the acute and/or post-acute phase, as was in our two patients. These may occur in individuals irrespective of the severity of the Covid-19 infection. Importantly, neurological findings in these patients may not be due to the underlying infection but as a consequence of it or may represent as a co-existing issue. Hence it is prudent for healthcare professionals to be aware of these so as to aid in the investigation and management of Covid-19 patients.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest in relation to this manuscript.

Statement of human and animal rights Not required.

Informed consent Informed written consent was obtained from both patients.

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