Cerebral microvascular injuries in severe COVID-19 infection: progression of white matter hyperintensities post-infection

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SUMMARY
A range of neuroradiological findings has been reported in patients with COVID-19, some mimicking cerebral small vessel disease (CSVD). We present a case of a man in his 50s with severe COVID-19, who was Glasgow Coma Scale 3 and tetraparetic after sedation was ceased in the intensive care unit. Return of consciousness and motor activity was slow. An MRI 1 month after debut of symptoms demonstrated white matter hyperintensities on T2-weighted Fluid Attenuated Inversion Recovery (T2-FLAIR) and many small areas with impaired diffusion in primarily supratentorial and infratentorial white matter on Diffusion-Weighted Imaging (DWI). In the following months, the patient made a remarkable clinical recovery. Despite clinical improvement, an MRI after 7 months showed that white matter hyperintensities had progressed and become confluent. Both MRIs demonstrated findings resembling CSVD, which could relate to a COVID-19-specific process affecting cerebral microvasculature.

BACKGROUND
A range of neuroradiological pathology has been reported in patients with COVID-19. In patients with COVID-19 with neurological symptoms, large and small vessel ischaemic and haemorrhagic stroke, cerebral microbleeds (CMB) and white matter hyperintensities (WMH) are frequently reported.1–3 Several case series have published neuroradiological findings on patients with COVID-19 with delayed wake-up, persistent coma and altered mental status. In addition to large and small vessel stroke, case series for such patients frequently describe CMB and diffuse WMH.1 Poor clinical outcomes were generally reported for this patient group.4–7 However, in a recent case report where extensive WMH were seen on acute MRI, there was remarkable clinical recovery in the months following severe COVID-19.8 Keller et al noted that radiological findings resemble those in cerebral small vessel disease (CSVD).3 The underlying pathology is unknown, but suggested mechanisms include hypoxia with delayed post-hypoxic leucoencephalopathy (DPhL), critical illness and SARS-CoV-2-specific mechanisms.2 3 8 Longitudinal studies with follow-up of patients with COVID-19 with the above clinical symptoms and radiological changes are scarce.

We present a patient with severe COVID-19, who was comatose (Glasgow Coma Scale (GCS) 3t) and tetraparetic after sedation was ceased on day 13 of mechanical ventilation. The initial MRI showed multiple small acute lacunar infarcts, widespread white matter lesions (often surrounding lacunar infarcts) and multiple CMB. The patient improved neurologically in the following months but had remaining cognitive deficits. Somewhat unexpectedly, a follow-up MRI after 6 months showed progression of white matter lesions on T2-weighted Fluid Attenuated Inversion Recovery (T2-FLAIR). In some previous reports, regression of leucoencephalopathy in connection with COVID-19 has been noted.1 9 However, in the case presented, there was substantial progress after recovery from infection.

CASE PRESENTATION
During the first wave of the corona pandemic in 2020, a man in his 50s with hypertension, obesity and chronic hepatitis B was admitted to hospital. The patient presented with severe dyspnoea and had a 10-day history of fever and cough. PCR test confirmed COVID-19 and CT of the chest showed extensive pulmonary changes with typical appearance for COVID-19 pneumonia.9 Laboratory tests at admission showed C reactive protein 358 mg/L and ferritin 2842 µg/L (table 1). The patient was directly admitted to the intensive care unit (ICU) and intubated (see figure 1 for timeline). He was hyperglycaemic at admission and diagnosed with diabetes mellitus type 2 (DM 2) after repeated plasma glucose measurements. The patient had a body mass index over 30 kg/m² for many years. Laboratory values were consistent with hyperosmolar hyperglycaemic and pronounced insulin resistance; there were no episodes of hypoglycaemia. Treatment included high-dose corticosteroids, dalteparin, broad-spectrum antibiotics, insulin, vasopressor medication and intravenous immunoglobulins. During ICU care, he developed acute kidney injury and continuous renal replacement therapy was initiated 1 week following admission. Subsequently, the patient developed hyperinflation and multiorgan failure during the second week in the ICU. He received one session of plasmapheresis after which clinical status and laboratory values improved. After 13 days of mechanical ventilation, sedation was withdrawn, but the patient remained comatose with GCS 3t (E1, V1, M1). Clinical assessment by a senior consultant in neurology showed tetraparesis and lack of reaction to pain but intact brainstem reflexes. Neurological deficits were considered secondary to a combination of hypoxic brain injuries and critical illness.
Case report

myopathy. An electroencephalogram demonstrated general slowing and decrease in wave amplitude, but no epileptic activity. After 34 days of total stay in the ICU, the patient had improved to GCS 5t (E3, V1t, M1), but remained tetraparetic and was moved to a high dependency unit. Here, motor activity returned partially to the distal aspects of the limbs. The level of consciousness improved to GCS 11t (E4, V1t, M6) 2 days prior to decannulation.

Two months post-admission, the patient was transferred to a brain injury rehabilitation ward. At this point, the patient had improved to GCS 15 and had been decannulated. However, he was bedridden and not able to perform any activities of daily living (ADL) independently. Over the subsequent months, his status improved remarkably. At discharge, the patient could perform ADL, with some assistance and walk 100 m with a walking aid. However, cognitive deficits relating to working and short-term memory were noted. At an outpatient appointment 6 months after symptom onset, on clinical examination, a minor paresis of the left foot and diminished peripheral reflexes were the only noted neurological deficits.

INVESTIGATIONS: RADIOLOGY

MRI (Siemens Magneton Skyra 3 T) of the brain including T1, T2, T2-FLAIR, Diffusion-Weighted Imaging (DWI), Apparent Diffusion Coefficient (ADC) and Susceptibility-Weighted Imaging (SWI) sequences was performed after 20 days in the ICU (around 30 days after COVID-19 symptom onset) and showed widespread pathology (figure 2). There was restricted diffusion (increased DWI signal and corresponding reduced ADC) in supratentorial and infratentorial areas bilaterally indicating acute/subacute ischaemic lesions. These were located primarily in the white matter, as well in the basal ganglia, thalami and cerebellum. Many lesions with decreased diffusion had surrounding

Table 1 Laboratory values of inflammatory markers

| Inflammatory marker | Value at admission | Value at 1 month (first MRI) | Highest value | Reference value | Unit |
|---------------------|--------------------|-----------------------------|--------------|----------------|------|
| CRP                 | 358                | 30                          | 429          | <3             | mg/L |
| D-dimer             | 0.46               | 4.6                         | 7.5          | <0.54          | mg/L |
| Ferritin            | 2843               | 5017                        | 98760        | 30–400         | µL   |
| IL-1β               | <5                 | 11.7                        | 32.4         | <5             | µg/mL|
| IL-6                | 76                 | 44                          | 875          | <5             | µg/mL|
| IL-10               | 9.4                | 13.4                        | 201          | <5             | µg/mL|
| Lactate dehydrogenase | 8.3              | 13.1                        | 166.9        | <3.5           | µkat/L|
| Platelets           | 201                | 105                         | 321          | 145–348        | ×10^9/L|
| Procalcitonin       | 0.23               | 4.8                         | 37           | <0.15          | µg/L |
| TNF-α               | 11.0               | 21.8                        | 66           | <12.0          | ng/L |
| WBC                 | 10.4               | 14.5                        | 34.7         | 3.5–8.8        | ×10^9/L|

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Figure 1 Timeline of clinical care. (A) Timeline of first 9 weeks of inpatient care. Horizontal lines, arrows and dots represent clinical interventions and treatments. (B) Overview of timeline from admission to second MRI brain at 7 months post-admission. Stars represent results from bacterial cultures. CRRT, continuous renal replacement therapy; HDU, high dependency unit; ICU, intensive care unit; IVIG, intravenous immunoglobulin; PEG, percutaneous endoscopic gastrostomy.
T2-FLAIR hyperintensities, particularly in the centrum semiovale. T2-FLAIR also showed WMH in the splenium of the corpus callosum and middle cerebellar peduncles bilaterally. Overall, deep WMH (DWMH) were graded 2–3 points according to Fazekas scale and periventricular hyperintensities (PVH) 2 points (table 2). Fazekas scale semiquantitatively grades lesions in brain deep and periventricular white matter from 0 (absence of lesion) to 3 (irregular PVH extending into the deep white matter for PVH and large confluent areas for DWMH, respectively). Additionally, an increased T1 signal was noted in globus pallidus bilaterally. Multiple susceptibility artefacts, suggestive of microhaemorrhages or microemboli, were seen in the frontal, parietal and temporal cortices, as well as in the external capsule and supratentorial white matter. No signs of cortical siderosis or subarachnoid haemorrhage were seen. Total small CSVD burden according to Staals et al was 2 points due to presence of susceptibility artefacts suggestive of microhaemorrhages and WMH. Seven months after COVID-19 symptom onset, a follow-up MRI (GE Healthcare Signa Artist 1.5 T) including T1, T2, T2-FLAIR, DWI-ADC and T2-Star-Weighted sequences was performed. It showed regression of areas with decreased diffusion. However, 10 of the areas with restricted diffusion at baseline in white matter had cavitated into lacunes. The increased T1 signal in globi pallidi had normalised. WMH on T2-FLAIR had expanded notably and become confluent in a large part of the deep cortical and periventricular white matter (figure 2, Fazekas scale 3 points for both DWMH and PVH). Despite clear clinical improvement, radiological CSVD increased between 1 and 7 months as graded by Fazekas score and total CSVD burden, while CMB burden remained relatively unchanged (table 2).

OUTCOME AND FOLLOW-UP
At 10 months after symptom onset, the patient had not been able to resume work. Neuropsychiatric tests at this time point (3 months after the second MRI) by an occupational therapist and psychologist demonstrated impairment in auditory verbal learning, memory recovery, processing speed, executive function and attention. In respect to diabetes management, insulin was suspended after 4 months and metformin was maintained. HbA1c was 47 mmol/mol at the time of the second MRI.

DISCUSSION
We report a case of severe COVID-19 with persistent coma after halted sedation, where the initial MRI showed small subcortical infarcts, widespread WMH and multiple susceptibility artefacts suggestive of microbleeds or microthrombi. Similar clinical symptoms and radiological findings have been reported previously. Remarkably, the patient’s neurological status improved to an unexpected degree in the months following critical care with only few remaining neurological deficits on clinical examination. Despite clear clinical improvement, a follow-up MRI 7 months after symptom onset demonstrated progression of WMH, engaging much of the supratentorial periventricular white matter.

The distribution of subcortical infarcts in our patient resembles a rosary-like watershed infarction pattern. The patient in our case suffered severe hypoxia when he arrived at the hospital prior to intubation and required vasopressors during care in the ICU to maintain haemodynamic stability. Gliosis following infarction likely partly accounts for the progress in hyperattenuation on T2-FLAIR at 7 months. Still, progression of WMH encompassed more extensive areas of supratentorial subcortical white matter than expected based on solely the areas of restricted diffusion at 1 month. We cannot exclude that additional cerebral insults occurred following the first MRI, or that pathology was already present which could not be visualised on the first MRI. However, following the first MRI, the patient had no further known episodes of significant haemodynamic instability, hypoxia or hypoglycaemia. Furthermore, WMH on T2-FLAIR progressed substantially over the next months, suggesting continued demyelination.

DPHL is a rare condition mainly described in connection to drug overdoses, carbon monoxide poisoning and other hypoxic episodes but rarely infection. However, our patient’s lesions in the basal ganglia and thalami are not typical for DPHL, and cerebellar lesions, multiple CMB and lacunar cavitations have not been previously described. Other explanations for WMH and multiple CMB after COVID-19 have been proposed. CMB are known to occur in critical illness, especially with respiratory failure. CMB have also been reported in patients with COVID-19, with or without leuкоencephalopathy. In an MRI case series of 10 mechanically ventilated patients with COVID-19 with respiratory failure, abundant CMB were seen in the corpus callosum.

The patient was diagnosed with DM 2 during ICU care. New-onset diabetes can occur in connection with COVID-19...
and is associated with poor prognosis.\(^{18}\) Our patient may have been pre-diabetic prior to contracting COVID-19, with stress hyperglycaemia and corticosteroid treatment contributing to diabetes onset. Diabetes may have influenced disease severity and hyperinflammation, but we consider it unlikely that plasma glucose levels directly contributed to subacute radiological findings and progression of WMH (plasma glucose 5.5–20.7 mmol/L before the first MRI and HbA\(_1c\) close to normal at follow-up).

Proposed explanations for observed MRI changes in patients with COVID-19 include direct SARS-CoV-2 infection, post-infectious encephalitis and vasculitis/endotheliitis.\(^{19} 20\) However, cerebrospinal fluid samples, when available, have not supported these diagnoses.\(^{5} 3\) In our case, afflicted areas of the brain are those supplied by small penetrating arteries and arterioles. An autopsy study of deceased patients with COVID-19 by Magro et al reported widespread microvascular thromboses in the brain which co-localised with endothelial injury, focal endothelial denudation, perivascular oedema and extravasation of red blood cells. Immunohistochemistry showed presence of the SARS-CoV-2 receptor ACE2 in afflicted microvessels. SARS-CoV-2 RNA was not detectable by in situ hybridisation; however, SARS-CoV-2 spike protein was demonstrated in ACE2-positive endothelial cells, possibly reflecting uptake of non-infectious pseudovirions. Microvessels with both ACE2 and spike protein displayed complement activation, inflammatory cytokines and markers of blood–brain barrier (BBB) dysfunction.\(^{19}\) Assuming a similar pathology in our patient, secondary effects of such microvascular injuries may cause long-term disturbances of the neurovascular-glia unit (NVGU) and/or nearby glia cells, such as astrocytes, microglia and oligodendrocytes. The notable expansion of WMH after SARS-CoV-2 infection suggests spreading of pathology, alternatively a long-term disturbance of perivascular fluid transport in the glymphatic system. Radiological findings and their evolution in the months following infection suggest cerebral COVID-19 may cause an accelerated form of CSVD,\(^{20}\) which for our patient was symptomatic with persistent cognitive deficits. Wenzel et al recently published findings of increased number of string vessels (capillaries with connective tissue lacking endothelium) in patients with COVID-19. They propose a pathophysiological mechanism for how SARS-CoV-2 induces string vessels/CSVD by production of viral protease Mpro cleaving NEMO. Loss of NEMO, a protective protein, was shown to result in reduced brain capillary endothelial cells associated with increased BBB permeability in a mouse model.\(^{21}\)

This case report has several limitations. Different MRI scanners with different resolutions were used for investigations at 1 and 7 months after COVID-19 symptom onset. Progression of CSVD features by several scoring systems was demonstrated but these were often already elevated on the first MRI. WMH volume may provide a better assessment of WMH progression. Had the follow-up MRI been performed with a 3 T scanner, rather than a 1.5 T scanner, more CMB may have been detected.\(^{22}\) Finally, there were several complications during and after ICU care, including sepsicaemia, hyperinflammation and multiorgan failure. These may have contributed to some of the radiological findings.

We present to our knowledge one of the first longitudinal follow-ups of a patient with persistent coma after severe COVID-19. A first MRI showed multiple lacunar infarcts, leuкоencephalopathy and multiple microbleeds, indicating widespread microvascular damage. Despite neurological improvement, MRI 6 months later showed progression of WMH on T2-FLAIR and the patient had remaining cognitive deficits. Radiological findings were not typical of hypoxia, DPHL or critical illness and are thought to reflect a SARS-CoV-2-specific pathology. Based on previous autopsy findings,\(^{19}\) we speculate that this pathology is caused by binding of SARS-CoV-2 spike protein to ACE2 on cerebral microvascular endothelial cells, but not necessarily active infection. Progression of WMH after COVID-19 may be due to secondary effects on the NVGU, glia cells or perivascular transport. Further research on patients with altered mental status after COVID-19 is warranted, including long-term clinical and radiological evaluation.

### Learning points

- Signs of cerebral microvascular pathology on MRI in the form of white matter hyperintensities and cerebral microbleeds are not uncommon in patients with severe COVID-19.
- Damage to cerebral microvasculature with microthrombosis, activation of inflammatory cascades and dysfunction of the blood–brain barrier have been reported in autopsy studies of brain tissue from patients with severe COVID-19.
- Neuroradiological signs of cerebral small vessel disease in patients with COVID-19 can be progressive and continue despite clinical improvement.
- Critically ill patients with COVID-19 with impaired consciousness and severe neurological symptoms can have improved clinical outcomes but may have cognitive sequelae.

### Contributors

The patient was under the care of AL. IP wrote and edited the manuscript and reviewed medical records. BMH provided radiological analysis and helped with writing and editing. AS reviewed the manuscript. AL oversaw and conceptualised the report and was involved in writing and editing the manuscript. AS participates in part of the DSMB of ProTEct-MS Trial.

#### Provenance and peer review

Not commissioned; externally peer reviewed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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