In patients with COVID-19, neurological complications are increasingly recognised, but only few neuropathological studies are available, documenting microthrombi and acute infarcts [1], hypoxic changes with no specific pathology [9] or perivascular lymphocytic infiltration in brainstem [10]. We report here neuropathology of two COVID-19 patients with findings in one strikingly similar to those described in a recent case report, with neocortical infarcts and small haemorrhagic and non-haemorrhagic white matter lesions [8], suggesting an emerging pattern of characteristic alterations, also observed radiologically [3].

Clinical data for both patients are provided in supplementary Fig. 1 and neuropathology and imaging in Figs. 1, 2 and supplementary Figs. 2, 3, 4.

Patient 1, a male in his fifties, suffered from cardiac arrest, shortly before veno-venous extracorporeal membrane oxygenation (vvECMO) and succumbed to multifocal brain infarcts. The ischaemic lesions in watershed areas are in keeping with sustained hypotension during cardiac arrest. The exact cause of the large right middle cerebral artery (MCA) and the bilateral posterior (PCA) infarcts remains uncertain. Thromboembolic origin from the known pulmonary embolus is excluded due to closed foramen ovale. The infarcts may be due to local thrombosis or, similar to watershed infarcts, may have developed as a complication of protracted hypotension during cardiac arrest. The florid leukocytoclastic reaction in the infarcts may simply be a reaction to reperfusion injury but may also be due to augmented immune response.

The second patient, a female in her sixties, was intubated and ventilated, but after discontinuing sedation, remained unresponsive and died due to multiorgan failure. The bilateral pallidal infarcts most likely were caused by hypoxia. Possible pathogeneses for the cortical and white matter microlesions, including microbleeds, include viral infection-related vascular injury; immune-mediated; or hypoxia...
secondary to hypotension, local thrombosis, or thromboemboli. MRI-pathology correlation showed that leptomeningeal hyperintensity corresponded to lymphohistiocytic inflammation. Microglial nodules, neuronophagia and vascular injury, including signs of vasculitis, distant from the infarcts were not identified in either case and inflammation in the medulla was similar to patients with a variety of other neurological diseases (supplementary Table 1, supplementary Fig. 4).

Several mechanisms for the SARS-CoV-2-related neurological complications are plausible. First, direct viral invasion via haematogenous or retrograde axonal route with intracellular accumulation either in endothelial cells, smooth muscle cells, pericytes, inflammatory cells (particularly macrophages), neurones or glial cells. Second, an indirect process resulting from hypercoagulability-related thromboembolism or thrombus formation within the brain or an exaggerated cytokine/immune-mediated response to viral infection causing damage to blood vessel walls or cells in the brain.

Viral components specifically in endothelial cells have been documented in kidney [7], lung and skin [5], but not with certainty in brain, although viral RNA of uncertain replicative and infective potential has been detected in the CSF [6] and brain tissue homogenates [7].

The few cases reported to date highlight the complexity of neuropathology in COVID-19 and the difficulty in untangling primary from secondary hypoxic/anoxic changes and iatrogenic aetiologies and suggest that a combination of

![Images of brain structures and infarcts](attachment:brain_diagram.png)
It is striking that ACE2 expression is increased in ischaemic brains and also in blood vessels in patients with diabetes [2], given that ACE2 represents the receptor by which...
SARS-CoV-2 enters host cells. Similarly, certain treatment regimens, such as ECMO, may increase the risk of neurological complications [4]. We provide further neuropathological correlates to a radiological feature of subcortical white matter microvascular lesions, including microhaemorrhages. Through future neuropathological studies, it is hoped that the mechanisms leading to tissue damage in COVID-19 will continue to be elucidated, to enable timely and appropriate treatment options.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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