LETTER TO THE EDITOR

Concentric demyelination pattern in COVID-19-associated acute haemorrhagic leukoencephalitis: a lurking catastrophe?

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We read with great interest the recent article by Paterson *et al*. entitled ‘The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings’ (Paterson *et al.*, 2020). The authors are to be congratulated for providing a comprehensive overview of the

neurologic manifestations associated with coronavirus disease 2019 (COVID-19). Five patients (Patients 13 to 17) were categorized within the spectrum of acute disseminated encephalomyelitis (ADEM) with haemorrhage. The latter consisted exclusively of microhaemorrhages documented by susceptibility-weighted MRI (SWI). In particular, microhaemorrhages were scarce in Patients 13 and 16, and numerous in Patients 14 and 15. However, though a diagnosis of ADEM was documented by brain biopsy in Patient 17, there was no MRI or histological evidence in favour of associated haemorrhage. SWI showed only medullary venous congestion secondary to the extensive hemispheric oedema, while smaller areas of hyperintense T_2 changes in the contralateral hemisphere were attributed to haemorrhagic foci without concomitant SWI confirmation. Paterson *et al*. (2020) suggested that Patient 17 complied to type II MRI pattern of brain white matter changes described by Kremer *et al.* (2020) in severe COVID-19. However, in this pattern, non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion were always associated with SWI-documented haemorrhage (Kremer *et al.*, 2020) and were not *per se* presumed to represent haemorrhagic foci. Consequently, we believe that a diagnosis of acute haemorrhagic leukoencephalitis was not sufficiently substantiated in Patient 17.

There is accumulating evidence of neurological complications in the context of COVID-19 (Zubair *et al.*, 2020). However, it is still unknown whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is neurotropic or mediates its CNS effects through para-infectious mechanisms. Moreover, neurological deficits in sedated patients under mechanical ventilation may be elusive and performing MRI in patients with COVID-19 in an intensive care unit (ICU) setting is complicated. Acute haemorrhagic leukoencephalitis (Weston Hurst syndrome, AHLE) is considered a fulminant variant of acute disseminated encephalomyelitis presumably induced by cross-reactivity between human myelin and viral or bacterial antigens (Gibbs *et al.*, 2005). We describe a case of COVID-19-associated AHLE with macroscopic haemorrhage, a particular localization and a concentric demyelination pattern in a critically ill patient.

A 57-year-old male had fever (37.5–39°C) and dry cough for 3 days. His arterial pressure was well controlled under irbesartan/hydrochlorothiazide and he did not smoke. A nasopharyngeal swab PCR result was positive for SARS-CoV-2 and he was admitted with bilateral peripheral infiltrates on chest X-ray. Written informed consent was obtained from the patient. He received azithromycin, hydroxychloroquine and lopinavir/ritonavir but 10 days later he deteriorated. We initiated mechanical ventilation along with interleukin-1 antagonist (anakinra 100 mg/day).

Over the following 10 days we recorded: elevated inflammatory marker values (CRP: 15 mg/dl, serum ferritin: 1000 ng/ml, procalcitonin: 1 ng/ml); relative (<15%) and absolute (<800/mm^3) lymphopenia; elevated D-dimers (>2000 ng/ml), normal fibrinogen (>200 mg/dl), prolonged international normalized ratio (INR; 1.3–1.5) and partial thromboplastin time (PTT; 60–80 s). As the respiratory parameters were improving we kept weaning the patient from sedation until complete withdrawal. Despite spontaneous eye opening, he remained flaccid and unconscious for more than 48 h until we noticed bilateral extension posturing on painful stimuli. His pupils were 3 mm but reactive to light, the horizontal vestibulo-ocular reflexes were blunted, deep tendon reflexes were exaggerated, and the plantar responses were indifferent. Brain CT showed bilateral subacute haemorrhagic lesions in the basal ganglia surrounded by oedema extending into the insula, the temporal and frontal lobe white matter, with sparing of the thalami (Fig. 1A). CT venography and angiography were unremarkable. MRI documented the presence of hemosiderin deposits (Fig. 1B–D) along with a concentric demyelination pattern (Fig. 1C and G). CSF was acellular with moderate protein elevation (0.69 g/l). IgG index was 0.51, oligoclonal bands were absent in CSF and serum, and PCR was negative for SARS-CoV-2, herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus (CMV), and Epstein-Barr virus. Blood and bronchoalveolar lavage fluid cultures were negative, and we retained a diagnosis of acute haemorrhagic leukoencephalitis (Weston Hurst syndrome). Under general supportive measures the patient recovered and 1 month later he only had moderate tetraparesis. A follow-up MRI showed oedema resorption and regression of the haemorrhagic lesions, which were involving exclusively white matter tracts (Fig. 1F and H).

Despite the absence of histologic confirmation, this case represents COVID-19-associated AHLE for the following reasons. First, MRI findings suggest haemorrhagic demyelination as the subjacent pathology. We documented multiple concentric zones of alternating hyperintensity and isointensity, along with separate rings of enhancement at sites of increased blood–brain barrier permeability, the hallmark of demyelination pattern encountered in Baló's concentric sclerosis (BCL) (Karaaslan *et al.*, 2001). BCL morphology is presumed to result from rings of 'benign' inflammation, which attempt to halt, albeit unsuccessfully, the expansion of a demyelination nidus (Mowry *et al.*, 2007). Concentric rings of demyelination alternating with rings of relatively preserved tissue are typically described in the histologic pattern III of multiple sclerosis, characterized by oligodendrocyte apoptosis and loss of myelin-associated glycoprotein. Interestingly, the latter white matter pathology can also be induced by

neurotropic viruses (HSV, CMV, JC virus) or by hypoxia-ischaemia (Aboul-Enein *et al.*, 2003).

As SARS-CoV-2 RNA was not detected in the CSF we cannot support a direct CNS invasion in our patient. Spread through the blood–brain barrier using immune cells expressing angiotensin-converting enzyme 2 (ACE2) receptors as a Trojan horse has been speculated for SARS-CoV-2 in analogy to SARS-CoV-1 (Zubair *et al.*, 2020). Additionally, COVID-19-associated systemic inflammation may impair blood–brain barrier permeability enhancing access of infected immune cells into the CNS. However, SARS-CoV-2 can infect, but not replicate, in T lymphocytes (Wang *et al.*, 2020) and hitherto, a direct viral effect on the brain has not been documented (Zubair *et al.*, 2020). On the other hand, *in vivo* activation of CD8+ T cells against a capsid antigen of Theiler's murine encephalitis virus (TMEV) has been shown to produce a model of AHLE in a non-demyelinating mouse strain (Pirko *et al.*, 2008). In this strain, the antiviral response is mediated by CD8+ viral epitope-specific T cells, resulting in effective TMEV clearance. Whether a similar activation of CD8+ T cells against SARS-CoV-2 epitopes would suffice to produce haemorrhagic demyelination in humans remains to be investigated.

Furthermore, in the setting of severe COVID-19 a combination of systemic hyperinflammation, hypercoagulability and endotheliopathy may result in impaired microcirculation, microvascular thrombosis, blood–brain barrier disruption and mitochondrial dysfunction. The subsequent hypoxic-ischaemic injury and the associated stress responses could contribute to a concentric demyelination pattern. Indeed, a unique interplay between hypoxia-induced tissue preconditioning and proinflammatory cytokines has been shown to contribute to the development of concentric lesions in Baló's disease (Stadelmann *et al.*, 2005; Takai *et al.*, 2016).

Second, our case is a pure leukoencephalopathy. Symmetric lesion localization in the external capsules is intriguing and may suggest a clustering of ACE2 expression, which determines potential SARS-CoV-2 cellular tropism in the CNS.

Our patient had a good clinical outcome along with a significant and relatively fast regression of the MRI lesions, which is rather counterintuitive. AHLE is associated with high mortality and heavy disability despite scarce reports of patients with minimal deficits after early and aggressive treatment (Gibbs *et al.*, 2005). Conversely, BCS is no longer considered a potentially lethal disease; still, lesions with a typical concentric pattern usually regress at a

slower pace (Karaaslan *et al.*, 2001). To our knowledge, there is no previous report of COVID-19-associated AHLE with overt haemorrhage, nor of a concentric demyelination pattern in AHLE. Therefore, it remains speculative whether the clinical and radiological recovery of our patient without receiving specific treatment is associated with the previous anakinra administration or with a *per se* favourable prognosis of COVID-19-associated AHLE. Our patient presents clinical similarities to Patients 13 and 14 reported by Paterson *et al.* (2020), who were slow to wake in the ICU. A recent retrospective observational study found that intracerebral haemorrhagic lesions were associated with a 5-fold rate of abnormal wakefulness when sedatives were stopped in critically ill patients with COVID-19 (Kremer *et al.*, 2020). Interestingly, both Patients 13 and 14 survived, albeit with sequalae, the former after purely supportive measures and the latter after receiving high-dose intravenous methylprednisolone for 3 days. We propose close neurological monitoring and imaging of ICU patients with COVID-19 during sedation withdrawal as neurological catastrophes may lurk in the absence of major respiratory compromise.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

References

Aboul-Enein F, Rauschka H, Kornek B, Stadelmann C, Stefferl A, Brück W, et al. Preferential loss of myelin-associated glycoprotein reflects hypoxia-like white matter damage in stroke and

inflammatory brain diseases. J Neuropathol Exp Neurol 2003; 62: 25-33. doi: 10.1093/jnen/62.1.25.

Gibbs WN, Kreidie MA, Kim RC, Hasso AN. Acute Hemorrhagic Leukoencephalitis: Neuroimaging Features and Neuropathologic Diagnosis. J Comput Assist Tomogr 2005; 29: 689-93. doi: 10.1097/01.rct.0000173843.82364.db.

Karaarslan A, Altintas A, Senol U, Yeni N, Dincer A, Bayindir C, et al. Baló's Concentric Sclerosis: Clinical and Radiologic Features of Five Cases. AJNR Am J Neuroradiol 2001; 22: 1362-7.

Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 2020: 202222. doi: 10.1148/radiol.2020202222.

Mowry EM, Woo JH, Ances BM. Technology insight: can neuroimaging provide insights into the role of ischemia in Baló's concentric sclerosis? Nat Clin Pract Neurol 2007; 3: 341-8. doi: 10.1038/ncpneuro0519.

Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020; awaa240. doi: 10.1093/brain/awaa240.

Pirko I, Suidan GL, Rodriguez M, Johnson AJ. Acute hemorrhagic demyelination in a murine model of multiple sclerosis. J Neuroinflammation 2008; 5:31. doi: 10.1186/1742-2094-5-31.

Stadelmann C, Ludwin S, Tabira T, Guseo A, Lucchinetti CF, Leel-Ossyet L, et al. Tissue Preconditioning May Explain Concentric Lesions in Baló's Type of Multiple Sclerosis. Brain 2005; 128: 979-87. doi: 10.1093/brain/awh457.

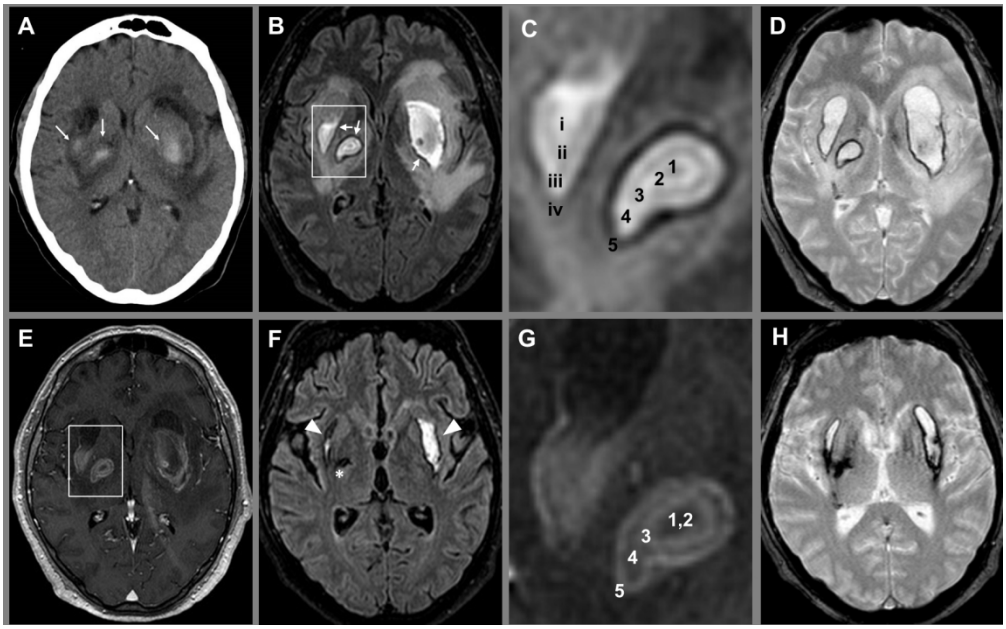
Takai Y, Misu T, Nishiyama S, Ono H, Kuroda H, Nakashima I, et al. Hypoxia-like Tissue Injury and Glial Response Contribute to Balo Concentric Lesion Development. Neurology 2016; 87: 2000-5. doi:.1212/WNL.0000000000003308.

Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cell Mol Immunol 2020. doi:10.1038/s41423-020-0424-

Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. JAMA Neurol 2020. doi: 10.1001/jamaneurol.2020.2065.

Figure legend

Figure 1 CT and MRI of the brain. (**A**) Non-contrast CT scan showing heterogeneous, hypoattenuating lesions in the basal ganglia bilaterally with confluent haemorrhagic elements (arrows). (**B**) Axial FLAIR MRI sequence demonstrating hypointense hemosiderin rims (arrows) and extensive perilesional oedema. Note sparing of the thalami. (**C**) Magnification of the area corresponding to the white frame showing a central isointense nidus (1) surrounded by alternating hyperintense (2, 4) and isointense (3) rings, consistent with concentric demyelination. The outermost ring (5) is hypointense corresponding to hemosiderin deposits. The adjacent lesion displays a similar lamellar pattern (i, ii, iii, iv). (**D**) Axial T_2* sequence documenting haemorrhage. (**E** and magnification of the area corresponding to the white frame in **G**) Axial T_1 MRI sequence after contrast infusion showing an alternating ring enhancement pattern. Note that layers 1 and 2 form a non-enhancing nidus surrounded by enhancing rings 3 and 5 and non-enhancing ring 4. (**F** and **H**) Axial FLAIR (**F**) and T_2* (**H**) MRI sequences 1 month later showing complete resorption of the perilesional oedema and comma-like residual lesions with a hemosiderin rim involving the external capsules (arrowheads) and the posterior limb of the internal capsule immediately adjacent to the globus pallidus (asterisk). Note the morphological integrity of all deep grey matter structures.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