Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Neuropathology associated with SARS-CoV-2 infection

We read with interest the Correspondence by Claus Hann von Weyhern and colleagues,[1] in which they report pronounced CNS involvement with pan-encephalitis in six patients with COVID-19 who were on invasive ventilation, some of whom were also receiving extracorporeal membrane oxygenation. Of these, three patients were further reported to have "massive intracranial" and "diffuse petechial haemorrhage in the entire brain".[1] These changes are then attributed directly or indirectly to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Having neuropathologically assessed brains of more than 41 patients with COVID-19, and having investigated the neurotropism of SARS-CoV-2, we do not concur with the conclusion that pan-encephalitis and CNS haemorrhage are common complications of COVID-19.[2,3] We do not observe pan-encephalitis, nor do we see massive intracranial haemorrhage or excessive and diffuse petechial haemorrhage in any of the brains of patients with COVID-19 that we have investigated (appendix).

See Online for appendix

It is well known that long-term intensive care involving invasive ventilation, and especially extracorporeal membrane oxygenation, can lead to intracranial haemorrhagic lesions and diffuse neuroimmune activation.[4] Additionally, immune activation should not be confused with encephalitis, and petechial haemorrhage routinely observed in brains of critically ill patients should not be over-interpreted as CNS haemorrhage. Moreover, other neuropathological studies of COVID-19 brains have not found any evidence of encephalitis or intracranial haemorrhage.[5]

Neuropathological assessment of patients with COVID-19, especially those dying under intensive care treatment, is an expert task and all observed changes must be carefully interpreted in the context of comorbidities and therapeutic interventions to avoid misinterpretation.

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3 Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020; **19:** 919–29.
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We believe that many of the key findings described in the Correspondence by Claus Hann von Weyhern and colleagues[1] should be interpreted differently. The exact nature of CNS involvement in COVID-19 is not only of fundamental importance for our understanding of the disease, but might have substantial consequences in directing clinical efforts to achieve better patient management in the future. Thus, observations about CNS inflammation as described by von Weyhern and colleagues will cause a great stir among biomedical scientists and clinicians if proven to be correct. However, we feel obliged to express our sincere reservations about the conclusions drawn from these data given the potentially wide-ranging consequences.

We particularly feel that the main conclusion, namely that "in addition to viral pneumonia, a pronounced CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage were key events",[1] are possibly the consequence of a misinterpretation of histological findings. Although it is conceivable that hypoxic-ischaemic neuronal damage could occur as part of COVID-19, the depicted neuronal changes characterised by contracted, intensely stained neurons do not represent hypoxic, but rather suggest dark neurons.[2] Dark neurons are frequent histological artifacts usually caused by post-mortem manipulation of the brain before fixation, and differ from dying or degenerating neurons.

Furthermore, we find the data illustrating the inflammatory involvement of the CNS in patients with COVID-19 unconvincing. Although we agree that a possible direct or indirect CNS involvement in the context of severe acute respiratory syndrome coronavirus 2 infection merits investigation, we cannot support the diagnosis made by the authors of pan-encephalitis or meningitis on the basis of the provided data and histological photomicrographs provided. We acknowledge the modest perivascular T-cell population depicted by immunohistochemistry by CD3 staining. However, such minimal lymphocytic CNS infiltrates are quite commonly seen in patients with multisystem failure (who required treatment in the intensive care unit), and we feel that these are non-specific changes whose clinical relevance is debatable. In our opinion, the histological findings have been over-interpreted as pan-encephalitis or meningitis. We would also highlight Solomon and colleagues' findings,[3] which are in line with our assessment (and also our observations of CNS COVID-19 autopsies performed at our centres), namely that encephalitis is not a general feature of COVID-19.

Although the global COVID-19 pandemic is a public health emergency and presents us with the need to find out as much as we can about the disease as rapidly as possible, we believe that hastily publishing such findings without adequate peer review should be challenged. Especially in times of description of a new disease, much care should be taken to obtain expert review of the findings and any conclusions need to be substantiated by appropriate evaluations and inclusion of controls. Although this literature draw attention to the important question of CNS involvement of COVID-19, the data presented by von Weyhern and colleagues are likely to cause confusion and possibly misdirect future clinical efforts.

We declare no competing interests.

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Claus Hann von Weyhern and colleagues[1] describe autopsy findings of six patients who died of COVID-19. Better understanding of the central effects of COVID-19 is crucial, and we read with great interest their findings that included pan-encephalitis and meningitis in all six patients, regardless of whether cause of death was due to cardiorespiratory failure, pulmonary embolism, or intracranial haemorrhage. However, the images provided in the appendix of the Correspondence[1] do not clearly show meningitis or encephalitis. Shrunken neurons are a common histological finding in autopsy brains and are often observed in neurologically normal cases without any specific pathological change, and the small cells indicated as infiltrating lymphocytes are difficult to distinguish from glial cells in the absence of an immunostain showing interstitial lymphocytes. For example, we show similar findings in a section of a normal neocortex (appendix). Although neuron loss was observed by von Weyhern and colleagues, neuronophagia and microglial nodules were not described. Additionally, perivascular lymphocytes are not diagnostic of viral meningitis or encephalitis but perhaps suggest that COVID-19 is associated with vascular alterations.

The findings of published cases and our own limited experience with COVID-19 disease pathology support that when brain pathology is present, it is apparently often associated with vascular changes, such as thrombi or thromboemboli, rather than primary involvement of the CNS. Although instances with neuropathology consistent with severe acute respiratory syndrome coronavirus 2 encephalitis have been reported, these changes are generally mild and variable.[2–4]

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Authors' reply

We welcome the opportunity to respond to the comments about our Correspondence.[1] To increase the availability of data, we reported our findings, which were produced by a team that included an experienced neuropathologist and was subjected to the *The Lancet*'s peer-review process. The three responses are similar as they all challenge our interpretation of the findings presented. Striking is the fact that the three responses disagree among themselves, with each offering yet another interpretation.

To analyse our findings, we consulted a standard neuropathology textbook, coauthored by one of our critics.[2] In the textbook, one reads that glial cells indeed can be differentiated from non-glial cells, and that hypoxic neurons can be distinguished from dark neurons based on classical haematoxylin and eosin staining.

In the absence of specific morphological alterations, shrinking is often the only indication of necrosis or apoptosis. Aware of the hypoxic origin of similar morphological alterations, we used the general level of hypoxic injury to vulnerable CA1 areas of the hippocampus and Purkinje cells in the cerebellum as a baseline. Because we did not observe hypoxic injury in these areas, we do not attribute the observed morphological alterations to hypoxia.

We concede that the term pan-encephalitis was poorly chosen. In the neuropathological literature, pan-encephalitis refers to a fulminant


Sean Gallup/Staff/Getty Images

See **Online** for appendix