Pearls and Oy-sters: Leukoencephalopathy in critically ill COVID-19 patients

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Pearls

- Coronavirus disease 2019 (COVID-19) can cause diffuse leukoencephalopathy.
- Though the pathophysiology of leukoencephalopathy due to COVID-19 is unclear at this time, there are a myriad of possible mechanisms for this finding including hypoxic ischemic injury, microvascular thrombosis secondary to hypercoagulability and endothelial damage.

Oy-sters

- Do not assume that critically ill patients with COVID-19 who are on sedation for a protracted period will be neurologically intact when sedation is discontinued and wears off.
- In critically ill patients with COVID-19 who have encephalopathy, before attributing prolonged coma to infection and toxic-metabolic conditions, obtain an MRI.
Introduction

The neurological manifestations of coronavirus disease 2019 (COVID-19) have been increasingly documented. However, severe encephalopathy with white matter changes on imaging has not been well described. We present four patients with leukoencephalopathy following COVID-19 infection that were evaluated by the neurology team at New York University Langone Health associated hospitals between April 2 and April 29, 2020. Select clinical data and laboratory values are found in Table 1 and Table e-1, http://links.lww.com/WNL/B187, respectively. All four cases were positive for SARS-CoV-2 nasopharyngeal PCR on admission.

Case Reports

Case 1

A 49-year-old man with a history of type II diabetes mellitus and thymoma presented to the emergency department (ED) with three days of cough. He developed hypoxic respiratory failure and required endotracheal intubation. He was empirically treated with hydroxychloroquine, azithromycin, zinc, and tocilizumab. He required multiple sedative agents for ventilator dyssynchrony. Neurology was consulted on hospital day 30, four days after discontinuation of sedation, because of persistent unresponsiveness. On evaluation, his eyes were open, but he did not attend, follow commands, or move his extremities in response to stimulation. MRI showed diffuse T2/FLAIR hyperintensities in the supratentorial white matter with diffusion restriction but no enhancement with gadolinium (Figure 1 A-C). Cerebrospinal fluid (CSF) studies were notable for elevated protein (147 mg/dL) without pleocytosis (3 cells/mL) and negative SARS-CoV-2 PCR. His serum neuron specific enolase level was 4.5 ug/L (reference range 3.7-8.9 g/L).
Serum myelin oligodendrocyte glycoprotein (MOG) antibody titer was <1:10. His mental status improved, such that he was able to follow one-step commands and answer simple yes or no questions on hospital day 41. His tracheostomy was decannulated on hospital day 51 and he was discharged to rehabilitation facility on day 69.

Case 2
A 73-year-old man with a history of coronary artery disease, Crohn’s disease, and prostate cancer with metastasis to the spine presented after one day of dyspnea, fever, and diarrhea. On hospital day nine, he was intubated for hypoxic respiratory failure. He received empiric treatment with hydroxychloroquine, azithromycin, tocilizumab, and nitazoxanide. He required multiple sedative agents throughout his hospital course, which were discontinued on hospital day 19, but he continued to be unresponsive. On neurological examination, he had spontaneous eye opening with intact pupillary light reflex and grimaced to noxious stimuli in all extremities. MRI of the brain showed confluent white matter hyperintensities in the fronto-parietal and temporoparietal lobes with associated diffusion restriction (Figure 1 D-F). Another brain MRI was performed 23 days later and showed stable findings. He made no improvement in neurological function and died on hospital day 60, two days after he was transitioned to comfort care.

Case 3
A 43-year-old morbidly obese man presented with seven days of progressive dyspnea, cough, fever, and generalized malaise. He was intubated for hypoxic respiratory failure and empirically treated with hydroxychloroquine, azithromycin, and tocilizumab. He required multiple sedative agents and neuromuscular blockade for ventilator dyssynchrony. On hospital day 29, he had
three generalized tonic-clonic seizures. Neurological examination revealed a lack of response to external stimuli and absent brainstem reflexes. MRI of the brain showed confluent T2/FLAIR hyperintensities involving the supratentorial and infratentorial white matter with associated diffusion restriction (Figure 1 G-I). He showed no neurological improvement and died of multiorgan failure on hospital day 38.

**Case 4**

A previously healthy 23-year-old man presented with five days of fever and encephalopathy. In the ED, he was somnolent, and his initial plasma glucose was 1,384 mg/dL. Metabolic acidosis resolved within 24 hours, but he remained obtunded. He was treated with hydroxychloroquine and azithromycin. Neurological exam was notable for unresponsiveness, extensor posturing to noxious stimulation in all extremities, and bilateral plantar extensor responses. EEG showed diffuse background slowing, but no seizures. MRI showed confluent T2/FLAIR hyperintensities with associated areas of diffusion restriction, but no enhancement with gadolinium, and two foci of microhemorrhages (Figure 1 J-L). On hospital day five, he required endotracheal intubation for hypoxic respiratory failure. He died on hospital day 10 of multiorgan failure.

**Discussion**

This case series highlights the potential for critically ill patients with COVID-19 to develop leukoencephalopathy that may only become clinically evident after sedation is withdrawn. Based on our current understanding of the pathophysiology of COVID-19, we discuss the possible mechanisms that could lead to leukoencephalopathy in these patients.
Patients with COVID-19 often develop a hypercoagulable state, as demonstrated by elevated D-dimer. Although neuropathological data in patients with COVID-19 is lacking, it is probable that these patients develop microvascular thromboses in the brain. There are areas of low T2/FLAIR signal at the center of many of the deep lesions in two cases, which may represent deoxyhemoglobin in dilated veins as a result of thrombosis in the deep venous system, but there is absence of enhancing transcerebral or medullary veins in the post-contrast sequences in the other cases.

Prolonged shock and refractory hypoxia in severe disease states can lead to cerebral hypoxic and ischemic injury, which likely also plays an important role in the development of these white matter changes. This can result in a diffuse leukoencephalopathy similar to delayed posthypoxic leukoencephalopathy, which would explain why these white matter changes are predominantly seen in watershed areas, though it is worth noting that the distribution of white matter changes is different from that which is typically seen in hypoxic brain injury.

Because elevated serum cytokine levels and inflammatory markers are hallmarks of severe COVID-19, these white matter changes could be the consequence of maladaptive systemic immune responses, as seen in acute necrotizing encephalopathy (ANE). However, our cases lack the symmetric thalamic lesions that are characteristic of ANE. The findings of punctate microhemorrhages in Case 4 prompted consideration of acute hemorrhagic leukoencephalitis (AHLE), but a more significant amount of hemorrhage would be expected with AHLE. Acute disseminated encephalomyelitis (ADEM) could also be considered, but the clinical course and
MRI findings in these cases are highly atypical for ADEM, which is characterized by asymmetric poorly demarcated lesions which occasionally show restricted diffusion.\textsuperscript{8}

The SARS-CoV-2 virus enters cells via angiotensin converting enzyme II (ACE2), which is expressed in the brain’s endothelial cells.\textsuperscript{1} Damages to the endothelial cells can lead to dysautoregulation of the cerebral vasculature resulting in capillary leak and further exacerbation of cerebral ischemia, creating a clinical picture that is akin to posterior reversible encephalopathy syndrome (PRES). Another possible explanation for this leukoencephalopathy is direct central nervous system (CNS) invasion by the virus causing encephalitis, though direct evidence of encephalitis secondary to SARS-CoV-2 is still lacking.\textsuperscript{1}

Finally, leukoencephalopathy may be due to toxic metabolic causes such as uremia and electrolyte disturbances. However, brain lesions associated with uremic encephalopathy preferentially involve the basal ganglia, and usually do not result in confluent bilateral white matter lesions.\textsuperscript{5} Extreme acute hyperglycemic and hyperosmotic states can lead to white matter lesions,\textsuperscript{9} but these conditions were only present in Case 4.

Of course, the small number of cases, absence of serial imaging and CSF results on all patients and lack of histopathological data limit our understanding of these findings.

**Conclusion**

A growing body of evidence suggests that SARS-CoV-2 has multiple deleterious effects on the CNS through various mechanisms.\textsuperscript{1} Our case series highlights the potential for patients with
severe cases of COVID-19 to develop diffuse white matter disease, which appears to be distinct from known diagnoses, and may represent a novel radiological pattern. In the critically ill COVID-19 population, it is important to avoid prematurely ascribing encephalopathy or coma to toxic-metabolic or other systemic causes, and to consider the possibility of structural brain damage. Longitudinal follow-up studies and histologic studies of brain tissue could help provide further insight.
## Appendix 1: Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>Hao Huang, MD</td>
<td>NYU Langone Health, New York, NY</td>
<td>Design and conceptualized study; analyzed the data; drafted and revised the manuscript for intellectual content; major role in the acquisition of data</td>
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<tr>
<td>Hillary Eichelberger, MD</td>
<td>NYU Langone Health, New York, NY</td>
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<td>Design and conceptualized study; analyzed the data; drafted and revised the manuscript for intellectual content; major role in the acquisition of data</td>
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<td>NYU Langone Health, New York, NY</td>
<td>Design and conceptualized study; analyzed the data; drafted and revised the manuscript for intellectual content; major role in the acquisition of data</td>
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<td>NYU Langone Health, New York, NY</td>
<td>Analyzed the data; revised the manuscript for intellectual content</td>
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<td>Analyzed the data; revised the manuscript for intellectual content</td>
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<td>Analyzed the data; revised the manuscript for intellectual content</td>
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<td>D. Ethan Kahn, DO</td>
<td>NYU Langone Health, New York, NY</td>
<td>Analyzed the data; revised the manuscript for intellectual content</td>
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<tr>
<td>Aaron Lord, MD</td>
<td>NYU Langone Health, New York, NY</td>
<td>Design and conceptualized study; analyzed the data; revised the manuscript for intellectual content; major role in the acquisition of data</td>
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<td>Ariane Lewis, MD</td>
<td>NYU Langone Health, New York, NY</td>
<td>Design and conceptualized study; analyzed the data; revised the manuscript for intellectual content; major role in the acquisition of data</td>
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</table>
References

Figure 1. MRI brain findings of patients with leukencephalopathy associated with COVID-19.

There are bilateral confluent areas of hyperintensity on T2 and FLAIR sequences (white arrows; A, D, G, J), associated with restricted diffusion restriction on DWI (arrowheads; B, E, H, K; ADC sequences with matching hypointensity are not shown). There are patchy areas of T2 and FLAIR hypointensity embedded in those lesions (asterisks; A, D). SWI sequences demonstrate no evidence of hemorrhage in Cases 1 to 3 (C, F, I) and rare foci of microhemorrhages in Case 4 on HemoFLASH (black arrows; L). MRI from Case 1 and Case 4 were performed with and without gadolinium contrast, but there is no associated gadolinium contrast enhancement nor evidence of venous sinus thrombosis (post-contrast sequences are not shown). 23 days after the initial MRI, Case 1 had a repeat MRI brain (not shown here) with stable findings, including confluent T2 lesions and restricted diffusion. FLAIR denotes fluid-attenuated inversion recovery, DWI diffusion weighted imaging, SWI susceptibility weighted imaging, HemoFLASH fast low angle shot gradient echo.
Table 1. Clinical Characteristics

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<td><strong>Age (years)</strong></td>
<td>49</td>
<td>73</td>
<td>43</td>
<td>23</td>
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<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td><strong>Timing of initial MRI (hospital day)</strong></td>
<td>33</td>
<td>31</td>
<td>31</td>
<td>5</td>
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<tr>
<td><strong>Days between symptom onset and MRI</strong></td>
<td>36</td>
<td>34</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td><strong>Days intubated before MRI</strong></td>
<td>33</td>
<td>22</td>
<td>31</td>
<td>0</td>
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<td><strong>Days on vasopressors before MRI</strong></td>
<td>27</td>
<td>12</td>
<td>7</td>
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<td><strong>Lowest oxygen saturation before MRI (%)</strong></td>
<td>52</td>
<td>83</td>
<td>80</td>
<td>93</td>
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<tr>
<td><strong>Days with MAP &lt;65</strong></td>
<td>6</td>
<td>2</td>
<td>6</td>
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<tr>
<td><strong>Lowest MAP before MRI</strong></td>
<td>54</td>
<td>54</td>
<td>43</td>
<td>76</td>
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<td><strong>Required dialysis prior to MRI</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td><strong>Sedation prior to MRI</strong></td>
<td>Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol</td>
<td>Dexmedetomidine, Fentanyl, Midazolam, Propofol</td>
<td>Fentanyl, Hydromorphone, Ketamine, Midazolam, Propofol, Cisatracurium</td>
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<td><strong>COVID-19 empiric treatment</strong></td>
<td>Hydroxychloroquine, Azithromycin, Zinc, Tocilizumab</td>
<td>Hydroxychloroquine, Azithromycin, Tocilizumab, Nitazoxanide</td>
<td>Hydroxychloroquine, Azithromycin, Nitazoxanide, Tocilizumab</td>
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<td><strong>Immunosuppressive treatment</strong></td>
<td>Intravenous methylprednisolone for 5 days</td>
<td>Prednisone 10 mg daily (long-term medication), then methylprednisolone 40 mg for 1 week, then hydrocortisone 25 mg every 12 hours for 3 days</td>
<td>No</td>
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<td><strong>Anticoagulation</strong></td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<td><strong>Antimicrobial treatment</strong></td>
<td>Amikacin, Cefepime, Clindamycin, Meropenem, Mica fungin, Vancomycin</td>
<td>Cefepime, Fluconazole, Levofloacin, Mica fungin, Piperacillin-tazobactam, Vancomycin</td>
<td>Ampicillin-sulbactam, Ceftriaxone, Meropenem, Piperacillin-tazobactam, Vancomycin</td>
<td>Ampicillin-sulbactam, Ceftriaxone, Piperacillin-tazobactam, Vancomycin</td>
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Neurologic exam at time of MRI

| Eyes open spontaneously, blink to threat present, extraocular movements intact, does not follow commands, grimaces in response to pain. | Eyes open to stimulation, pupils reactive, does not track, grimaces to pain. | Sedated, no response to noxious stimulation, no brainstem reflexes. | Eyes open to noxious stimulation, pupils reactive, gaze midline, no blink to threat, extensor posturing to noxious stimuli, plantar extensor response. |

Outcome at Time of Publication

| Rehabilitation Facility | Deceased | Deceased | Deceased |

CSF Studies

| WBC 3/uL; Protein 147 mg/dL; Glucose 62 mg/dL; PCR assay neg SARS-CoV-2; oligoclonal bands negative; CSF angiotensin converting enzyme 1.7 U/L; Flow cytometry no evidence of non-Hodgkin lymphoma and no evidence of chronic neuroinflammatory process. | Not obtained | Not obtained | Not obtained |

Abbreviations: MRI denotes magnetic resonance imaging, ICU intensive care unit, CSF cerebrospinal fluid, WBC white blood cell count.
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