Acute Hemorrhagic Leukoencephalopathy Triggered by COVID-19 Infection

Maria L Benevides, MD, PhD, Stefany Elias, Diego A Fagundes, MD, Rafael F Martins, MD, Michel M Dutra, MD, PhD, Maria E Rodrigues de Oliveira Thais, PhD, Gabriel M Rodrigues, MD, Jean C Nunes, MD, PhD, and Gladys L Martins, MD

Abstract
Background: This study represents an additional case of a rare entity and complication of COVID-19. Purpose: To further describe COVID’s association with acute hemorrhagic leukoencephalopathy (AHL), a variant of acute disseminated encephalomyelitis. Besides, subsequent neuropsychological evaluation is described. Methods: The present case report describes clinical, laboratory, radiological, and electroencephalographic characteristics of AHL triggered by COVID-19, in addition to outcomes in the neuropsychological findings. Results: Radiologic findings of demyelinating lesions in supratentorial white matter permeated by multiple hemorrhagic foci supported the diagnosis of AHL, reinforced by clinical improvement after corticosteroid therapy. Conclusions: There are few similar cases previously reported, and this case highlights the early diagnosis and prompt treatment looking forward to better outcomes in AHL. Further studies are needed to elucidate the involved pathophysiological mechanisms.

Keywords
COVID-19, SARS-CoV-2, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalopathy

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generates a multiorgan inflammatory response and endothelial dysfunction that might lead to a wide range of neurological disorders.1 Thus far, case reports have shown COVID-19 patients presenting with encephalopathies, acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome, strokes, and posterior reversible encephalopathy syndrome (PRES).2 The mechanisms are still unclear; however, some hypotheses have been considered, such as SARS-CoV-2 invasion in CNS cells, epithelial–endothelial barrier disruption, inflammation, coagulopathy, and post-infectious manifestations due to various immune-mediated processes.2 This study represents an additional case of a rare entity and complication of COVID-19, and aims to further describe COVID’s association with acute hemorrhagic leukoencephalopathy (AHL), a variant of ADEM. Besides, subsequent neuropsychological evaluation is described.

Case Description
A previously healthy 50-year-old Caucasian woman, an elementary school teacher, presented to the emergency department with two episodes of focal to bilateral tonic-clonic seizures separated by less than 24 h. Over the previous 3 days, she had been presenting with myalgia, fever, nausea, vomiting, and severe headache. She did not have respiratory symptoms or hypoxemia. On neurological examination, she was confused and disorientated, alternating periods of psychomotor agitation and apathy. She had no cranial nerve, sensorial, and muscular function impairments. Deep tendon reflexes were normal, and pathologic reflexes were absent.
Coordination and gait were normal. Neck rigidity was present, but Kernig and Brudzinski’s signs were absent. Multiorgan clinical evaluation was unremarkable.

On laboratory assessment, she presented with slight elevation of transaminases, lymphocytopenia, elevated D-dimer, and ferritin. Serological tests for human immunodeficiency virus (HIV), hepatitis C and B, and syphilis were negative. There was no clinical evidence of systemic vasculitis, and the antinuclear antibody was negative. Reverse transcription real-time quantitative polymerase chain reaction (RT-qPCR) for SARS-CoV-2 was positive on nasopharyngeal specimens, and rapid immunoglobulin G and M serological tests were negative. Cerebrospinal fluid (CSF) analysis showed 8 cells/mm³, with neutrophil predominance (60%), 768 erythrocytes/mm³, proteins were 150 mg/dL, glucose was 67 mg/dL (blood glucose 120 mg/dL), lactic dehydrogenase was increased (43 U/L), and cultures for bacteria and fungi were negative. Xanthochromia was not observed; CSF was initially slightly cloudy but clarified after centrifugation. Besides, erythrocyte count was not persistently elevated. A control CSF analysis, with a 4-day interval, showed 277 erythrocytes/mm³. RT-qPCR for SARS-CoV-2 on CSF was negative. Herpes panel was also negative, including Herpes simplex 1 and 2, Varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Immunoglobulin, IgG index, IL-6, and anti-MOG were not available and not tested since resources have been limited during pandemic.

Brain magnetic resonance imaging (MRI) at 1.5-tesla unit showed hypointense lesions on the right temporal lobe, left parietal lobe, and both occipital lobes in susceptibility-weighted imaging (SWI) suggesting hemorrhagic lesions. Fluid-attenuated inversion recovery (FLAIR) demonstrated hyperintense surroundings, reflecting significant edema. Thalami were spared, but hippocampal formations were altered (Figure 1). There was no contrast enhancement. No vessel abnormality was observed on CT angiography.

Scalp electroencephalogram (EEG) was also performed and showed generalized rhythmic delta activity (GRDA) with low voltage rhythmic background activity.

The clinical, laboratory, and imaging characteristics suggested the diagnosis of AHL, a clinical subtype of ADEM. Intravenous methylprednisolone (IVMP) 1 g per day was
prescribed on the third day of admission, for 5 days. After treatment, the patient progressed with remarkable clinical and consciousness improvement.

On one-month follow-up evaluation, she was submitted to a complete neuropsychological evaluation, which encompassed several cognitive tests. The results showed subtle working memory, arithmetic, attention, and fluency deficits. Those scores reached the low average. Besides, she was diagnosed with severe anxiety. A new brain MRI revealed a significant improvement in cerebral lesions (Figure 2); and the EEG also improved.

**Discussion**

The present study describes a case of a previously healthy woman presenting with acute neurological manifestations and radiologic findings compatible with an inflammatory demyelinating disease of supratentorial white matter, permeated by hemorrhagic foci, favoring the diagnosis of AHL, an ADEM variant. Considering the chronologic relation between SARS-CoV-2 infection and the onset of symptoms, the possibility of SARS-CoV-2 as a trigger of the inflammatory process is reinforced. There are few similar cases reported in the literature, most of them manifesting without hemorrhagic features.2-3 ADEM is a demyelinating disease of the central nervous system (CNS) often preceded by a viral infection, characterized by an acute or subacute encephalopathy.4 ADEM is histologically defined by perivenular inflammatory infiltrates and adjacent demyelination, with the presence of T cells and macrophages.3-4 The hemorrhagic variants have a pronounced neutrophilic infiltrate,3 which might explain the predominance of neutrophils in CSF analysis in the presented case. Those alterations are believed to be associated with an immunological process related to molecular mimicry.4 The present case makes that hypothesis reasonable since RT-qPCR for SARS-CoV-2 in CSF was negative, and considering other inflammatory disruptions caused by COVID-19.1-2 Moreover, it might be possible that an early viral parenchymal invasion had preceded an immune response. Interestingly, AHL may be reported more frequently with COVID-19 than other viral illnesses.
Besides, considering the physiopathology of the AHL variant of ADEM, the elevation of CSF cytokines, such as interleukins (IL), is related to lymphocytes, neutrophils, and innate immune cells recruitment.\textsuperscript{5} Those findings suggest how the SARS-CoV-2 might disrupt the immunological system and lead to neurological impairments, since T lymphocytes, neutrophils, and IL-6 are known to play an important role in COVID-19.\textsuperscript{1}

In differential diagnosis, regarding the spectrum of demyelinating diseases, the Marburg variant was considered due to the acute onset of diffuse demyelinating lesions, but due to the excellent clinical outcome was thought to be an unlikely diagnosis.\textsuperscript{5} Secondly, viral encephalitis caused by SARS-CoV-2 is unlikely since the RT-qPCR in CSF was negative; however, the sensitivity of this test is questionable since the diagnostic assays are still emerging and the accuracy of tests varies widely.

Moreover, Acute Necrotizing Encephalopathy (ANE) should be considered as another differential diagnosis. ANE is a post-viral inflammatory disease, characterized by symmetric lesions in grey and white matter, and bilateral thalamic involvement.\textsuperscript{4} In addition, the CSF usually shows an increased protein without pleocytosis.\textsuperscript{4} The present case favors that diagnosis since the radiological cerebral lesions were asymmetric and thalami were spared, and CSF analysis demonstrated neutrophilic pleocytosis and increased erythrocytes.\textsuperscript{3,4}

This study is an additional case of a rare complication of COVID-19. Previous systematic-review studies have identified a total of 14 cases of AHL,\textsuperscript{4,5} until November 2021. Based on the physiopathology, and previous AHL cases associated with other viral triggers, most patients with AHL triggered by COVID-19 were treated with IVMP, frequently followed, or concomitant to intravenous immunoglobulin.\textsuperscript{2,3} Plasmapheresis and azithromycin combined with hydroxychloroquine have been administered to two AHL patients.\textsuperscript{5} Other immunotherapies, such as rituximab, ocrelizumab, and cyclophosphamide, have been used in a few patients diagnosed with ADEM, not AHL.\textsuperscript{2} Outcomes varied: four of them were ongoing at the time of the studies, four deceased, one data was not shown, and others partially improved, requiring rehabilitation.\textsuperscript{3}

The present case differs from previous cases reported in the literature\textsuperscript{2,3,6-14} since it describes neuropsychological features after 1 month, and showed an excellent outcome, except for some residual working memory, arithmetic, attention, and fluency deficits. Some characteristics might explain this outcome, such as early treatment and not presenting with respiratory symptoms.

This case illustrates the clinical, laboratory, radiological, and electroencephalographic characteristics that supported the diagnostic of AHL variant of ADEM triggered by COVID-19, which was reinforced by clinical improvement after corticosteroid therapy. There are a few cases reported in the literature\textsuperscript{2,3,6-14} and the present case highlights the importance of the early diagnosis for prompt treatment to better outcomes. Further studies are needed to elucidate the mechanisms involved in ADEM variants when triggered by SARS-CoV-2.

Acknowledgment
Written informed consent was obtained from the patient.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Availability of Data and Material
Authors had full access to all of the data that support the findings of this study, which are available on request from the corresponding author.

ORCID iD
Maria L Benevides  https://orcid.org/0000-0001-8992-4418

References
Wiersinga WJ, Rhodes A., Cheng A. C., Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus disease 2019 (COVID-19). JAMA. 2020;324:782–793. doi: 10.1001/jama.2020.12839.

Wang Y, Wang Y, Huo L, Li Q, Chen J, Wang H. SARS-CoV-2-associated acute disseminated encephalomyelitis: A systematic review of the literature. J Neurol 2021;1–22. doi:10.1007/s00415-021-10771-8. https://doi.org/10.1007/s00415-021-10771-8.

Manzano GS, McEntire CRS, Martinez-Lage M, Mateen FJ, Hutto SK. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis following COVID-19: Systematic review and meta-synthesis. Neurul Neuroinmunol Neuroinflamm. 2021;8(6):e1080. doi:10.1212/NXI.0000000000001080.

Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis following COVID-19: Systematic review and meta-synthesis. Neurology. 2016;87:S38-S45. doi:10.1212/WNL.0000000000002825.

Waak M, Malone S, Sinclair K, et al. Acute hemorrhagic leukoencephalopathy: Pathological features and cerebrospinal fluid cytokine profiles. Pediatr Neurol. 2019;100:92–96. doi:10.1016/j.peditrneurol.2019.06.013.

Yong MH, Chan YFZ, Liu J, et al. A rare case of acute hemorrhagic leukoencephalitis in a COVID-19 patient.
Chalil A, Baker CS, Johnston RB, et al. Acute hemorrhagic encephalitis related to COVID-19. Neurol Clin Pract. 2021;11:e147–e151. doi:10.1212/CPJ.0000000000000900.

Handa R, Nanda S, Prasad A, et al. Covid-19-associated acute haemorrhagic leukoencephalomyelitis. Neurol Sci. 2020;41(11):3023–3026. doi:10.1007/s10072-020-04703-z.

Karapanayiotides T, Geka E, Prassopoulos P, et al. Concentric demyelination pattern in COVID-19-associated acute haemorrhagic leukoencephalitis: A lurking catastrophe? Brain. 2020;143(12):e100. doi:10.1093/brain/awaa375.

Ghosh R, Dubey S, Finsterer J. SARS-CoV-2-associated acute hemorrhagic, necrotizing encephalitis (ahne) presenting with cognitive impairment in a 44-year-old woman without co-morbidities: A case report. Am Journal Case Reports. 2020;21:e925641. doi:10.12659/AJCR.925641.

Perrin P, Collongues N, Baloglu S, et al. Cytokine release syndrome-associated encephalopathy in patients with COVID-19. Eur J Neurol. 2021;28(1):248–258. doi:10.1111/ene.14491.

Walker JM, Gilbert AR, Bieniek KF, Richardson TE. COVID-19 patients with CNS complications and neuropathologic features of acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalopathy. J Neuropathol Exp Neurol. 2021;80(6):628-631. doi:10.1093/jnen/nlab036.

Varadan B, Shankar A, Rajakumar A, et al. Acute hemorrhagic leukoencephalitis in a COVID-19 patient-a case report with literature review. Neuroradiology. 2021;63(5):653–661. doi:10.1007/s00234-021-02667-1.

Haqiqi A, Samuels TL, Lamb FJ, et al. Acute haemorrhagic leukoencephalitis (Hurst Disease) in severe COVID-19 infection. Brain Behav Immun Health 2021;12:100208. doi:10.1016/j.bbih.2021.100208. https://doi.org/10.1016/j.bbih.2021.100208.