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VIEWS AND REVIEWS

COVID-19 associated brain/spinal cord lesions and leptomeningeal enhancement: A meta-analysis of the relationship to CSF SARS-CoV-2

Ariane Lewis[1,2] | Rajan Jain[2,3] | Jennifer Frontera[1,2] | Dimitris G. Placantonakis[2] | Steven Galetta[1,4] | Laura Balcer[1,4,5] | Kara R. Melmed[1,2]

[1] Department of Neurology, NYU Langone Medical Center, New York, New York, USA

[2] Department of Neurosurgery, NYU Langone Medical Center, New York, New York, USA

[3] Department of Radiology, NYU Langone Medical Center, New York, New York, USA

[4] Department of Ophthalmology, NYU Langone Medical Center, New York, New York, USA

[5] Department of Population Health, NYU Langone Medical Center, New York, New York, USA

Correspondence
Ariane Lewis, MD, Departments of Neurology and Neurosurgery, NYU Langone Medical Center, 530 First Avenue, HCC-5A, New York, NY 10016, USA.
Email: Ariane.Kansas.Lewis@gmail.com

ABSTRACT

Background and Purpose: We reviewed the literature to evaluate cerebrospinal fluid (CSF) results from patients with coronavirus disease 2019 (COVID-19) who had neurological symptoms and had an MRI that showed (1) central nervous system (CNS) hyperintense lesions not attributed to ischemia and/or (2) leptomeningeal enhancement. We sought to determine if these findings were associated with a positive CSF severe acute respiratory syndrome associated coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR).

Methods: We performed a systematic review of Medline and Embase from December 1, 2019 to November 18, 2020. CSF results were evaluated based on the presence/absence of (1) ≥ 1 CNS hyperintense lesion and (2) leptomeningeal enhancement.

Results: In 117 publications, we identified 193 patients with COVID-19 who had an MRI of the CNS and CSF testing. There were 125 (65%) patients with CNS hyperintense lesions. Patients with CNS hyperintense lesions were significantly more likely to have a positive CSF SARS-CoV-2 PCR (10% [9/87] vs. 0% [0/43], $p = 0.029$). Of 75 patients who had a contrast MRI, there were 20 (27%) patients who had leptomeningeal enhancement. Patients with leptomeningeal enhancement were significantly more likely to have a positive CSF SARS-CoV-2 PCR (25% [4/16] vs. 5% [2/42], $p = 0.024$).

Conclusion: The presence of CNS hyperintense lesions or leptomeningeal enhancement on neuroimaging from patients with COVID-19 is associated with increased likelihood of a positive CSF SARS-CoV-2 PCR. However, a positive CSF SARS-CoV-2 PCR is uncommon in patients with these neuroimaging findings, suggesting they are often related to other etiologies, such as inflammation, hypoxia, or ischemia.

KEYWORDS
cerebrospinal fluid, COVID-19, MRI, neuroinvasion, SARS-CoV-2

INTRODUCTION

Patients with coronavirus disease 2019 (COVID-19) who have neurological symptoms often have central nervous system (CNS) hyperintense lesions and/or leptomeningeal enhancement on neuroimaging.[1–6] Postulated mechanisms for these findings include ischemia, inflammation, anoxia, and viral neuroinvasion. Cerebrospinal fluid (CSF) testing is one means to evaluate for viral neuroinvasion via (1) the severe acute respiratory syndrome associated coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) assay or (2) testing

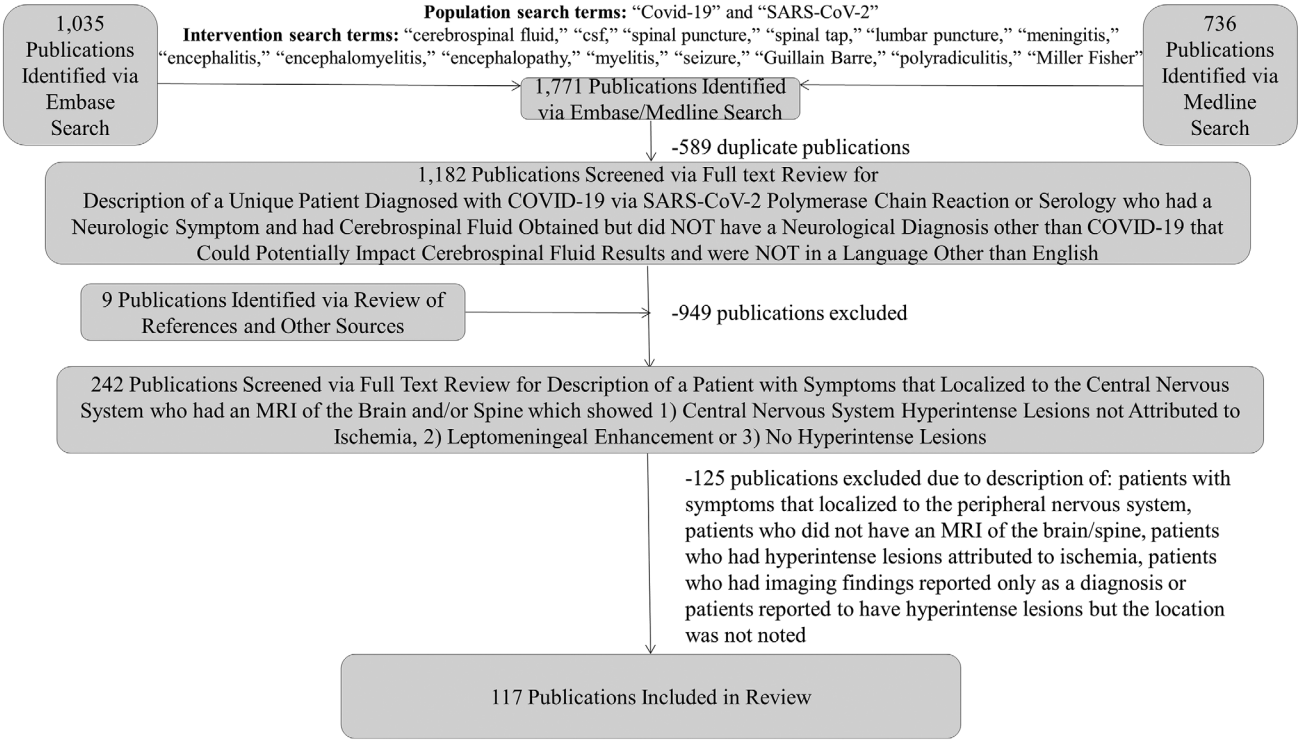


FIG 1 Publication selection

for intrathecal SARS-CoV-2 antibody production.[7] We sought to determine whether CNS hyperintense lesions and leptomeningeal enhancement on magnetic resonance imaging (MRI) of the brain or spine in patients with COVID-19 is associated with evidence of SARS-CoV-2 in the CSF.

METHODS

In a larger systematic review, two board-certified neurologists screened 1182 publications obtained via a search of Medline and Embase from December 1, 2019 and November 18, 2020 using the population search terms "COVID-19" or "SARS-CoV-2" and the intervention search terms "cerebrospinal fluid" or "csf" or "spinal puncture" or "spinal tap" or "lumbar puncture" or "meningitis" or "encephalitis" or "encephalomyelitis" or "seizure" or "encephalopathy" or "myelitis" or "Guillain Barre" or "polyradiculitis" or "Miller Fisher" and identified 242 publications in English that described a unique patient diagnosed with COVID-19 via SARS-CoV-2 PCR or serology who had a neurological symptom and had CSF results reported, but did not have a diagnosis that could impact CSF results, such as subarachnoid hemorrhage or another intracranial infection.[7] These publications were subsequently screened to identify those that described a patient who had symptoms that localized to the CNS, had an MRI of the brain and/or spine, and whose MRI showed (1) CNS hyperintense lesions (on a T2/fluid-attenuated inversion recovery sequence, if specific sequences were specified) that the authors of the case report/case series did not attribute to acute/chronic ischemia and/or (2) leptomeningeal enhancement or (3) no CNS hyperintense lesions (to serve as a comparator group). It was not feasible to review all sequences and images of the MRIs ourselves, so we relied on the authors' reports of the MRI findings, though a board-certified neurologist and/or neuroradiologist reviewed the imaging sequences that were included in the publications. Publications were excluded if they did not describe a patient who had symptoms that localized to the CNS or an MRI of the brain/spine, or whose MRI (1) showed CNS hyperintense lesions attributed to ischemia; (2) showed findings that were reported as a diagnosis rather than described, such as "acute disseminated encephalomyelitis;" or (3) was noted to have CNS hyperintense lesions with no mention of the location of these lesions. This resulted in identification of 117 publications that met inclusion criteria. This search was performed in accordance with PRISMA guidelines (Figure 1).[8]

Cases that met inclusion criteria were reviewed and patients were classified based on the presence of CNS hyperintense lesions and leptomeningeal enhancement (if a contrast MRI was performed). Patients with CNS hyperintense lesions were organized based on lesion location (cortical, limbic, subcortical/deep white matter, basal ganglia/thalamic, corpus callosum, brainstem/cerebellum/spinal cord; Figure 2), while those with leptomeningeal enhancement were categorized based on whether the enhancement was focal or diffuse (as delineated by the authors or if noted to be present bilaterally and/or in >1 location). Patients with CNS hyperintense lesions in >1 location were categorized based on each individual location that had lesions and also included in a separate category for patients with multifocal CNS hyperintense lesions. For patients who had >1 MRI, the findings

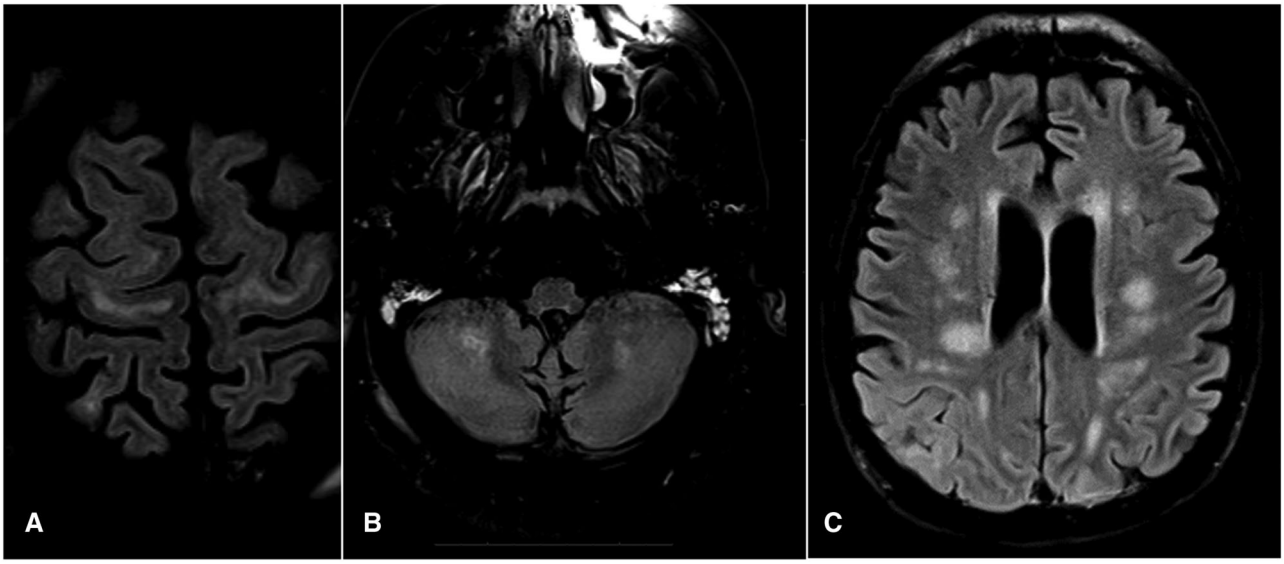


FIG 2 Central nervous system hyperintense lesions in patients with COVID-19 at our institution in the (A) subcortical white matter, (B) cerebellum, and (C) subcortical/deep white matter

from all scans were included when documenting presence and location of CNS hyperintense lesions and leptomeningeal enhancement. For patients who had >1 lumbar puncture, the findings from all CSF samples were included and the highest CSF white blood cell (WBC) count and CSF protein were reported. The CSF studies were conservatively considered to demonstrate evidence of SARS-CoV-2 if there was (1) a single positive CSF SARS-CoV-2 PCR; or (2) antibody, oligoclonal band, or immunoglobulin findings suggestive of intrathecal antibody synthesis in the absence of an identified autoimmune antibody in the CSF.[7] Severity of COVID-19 infection was determined based on the World Health Organization's criteria.[9] All laboratory test results were converted to a common unit to facilitate comparison.

The CSF results were compared for patients who had ≥ 1 CNS hyperintense lesion to patients with no CNS hyperintense lesions and for patients who had leptomeningeal enhancement to patients who had no leptomeningeal enhancement on an MRI with contrast. Additionally, the CSF results for patients who had CNS hyperintense lesions at each location were compared to those from patients who had an MRI brain who did not have lesions in the location being reviewed (e.g., CSF from patients with cortical hyperintense lesions were compared to CSF from patients who had an MRI brain and did not have cortical hyperintense lesions). Lastly, the CSF results from (1) patients with multifocal CNS hyperintense lesions were compared to those from patients who had an MRI brain and only had unifocal CNS hyperintense lesions and (2) patients with focal leptomeningeal enhancement were compared to those from patients with diffuse leptomeningeal enhancement. Comparisons were made using Chi-square and Fisher tests as appropriate using IBM SPSS Statistics Version 25. A p-value <0.05 was considered statistically significant.

RESULTS

Patient identification

After review of the 117 publications, we identified 193 patients who met inclusion criteria.[1,2,10–124] There were 105/189 (56%) male patients.[1,2,10–12,14,16,17,19,22,26,27,31,33,35,37–40,46,47,50,51,54,57–60,62,64–71,75,76,79,81,82,84,85,87,89,91,93,95–97,99,101–105,107–109,113–120,124] The median age was 56 (range 2–96) years old.[1,2,10–122,124] There were 79/167 (47%) patients with severe COVID-19.[1,2,10–12,14–16,18,22,26,33,36,40–44,49,51–53,55,58,61,63,70,71,77,80,81,87–89,95,96,99,108,116,117,121–123] Of 154 patients with outcome data reported, 22 (14%) died before their case was published.[1,10,14,16,33,39,49,51,55,57,61,64,81,82,84,89,96,123]

MRI and CSF acquisition

The primary neurological symptoms that precipitated MRI and CSF acquisition are shown in Figure 3; for the majority of patients (144, 75%), this workup was performed due to coma/encephalopathy with or without seizure/abnormal movement/headache.[1,2,11,12,14–16,22,23,26,33,36,39–42,44–48,50,51,53–57,61,63–73,75–84,87,88,90–92,94–105,108,109,111–119,121–123]

Although the number of days between the MRI and lumbar puncture was only specified for the minority of patients (41, 21%), among those where it was, there was a median of 0 (interquartile range [IQR] −2 to 0) days between the MRI and lumbar puncture.[15,16,18,23,33,40,45,47,51,53,55,60,61,67,73,76–78,81,87,91–93,98,100–102,109,116,118,119,121]

There were 17 (9%) patients with CSF cell count, protein, SARS-CoV-2 PCR or antibody results from >1 lumbar puncture and 34 (18%)

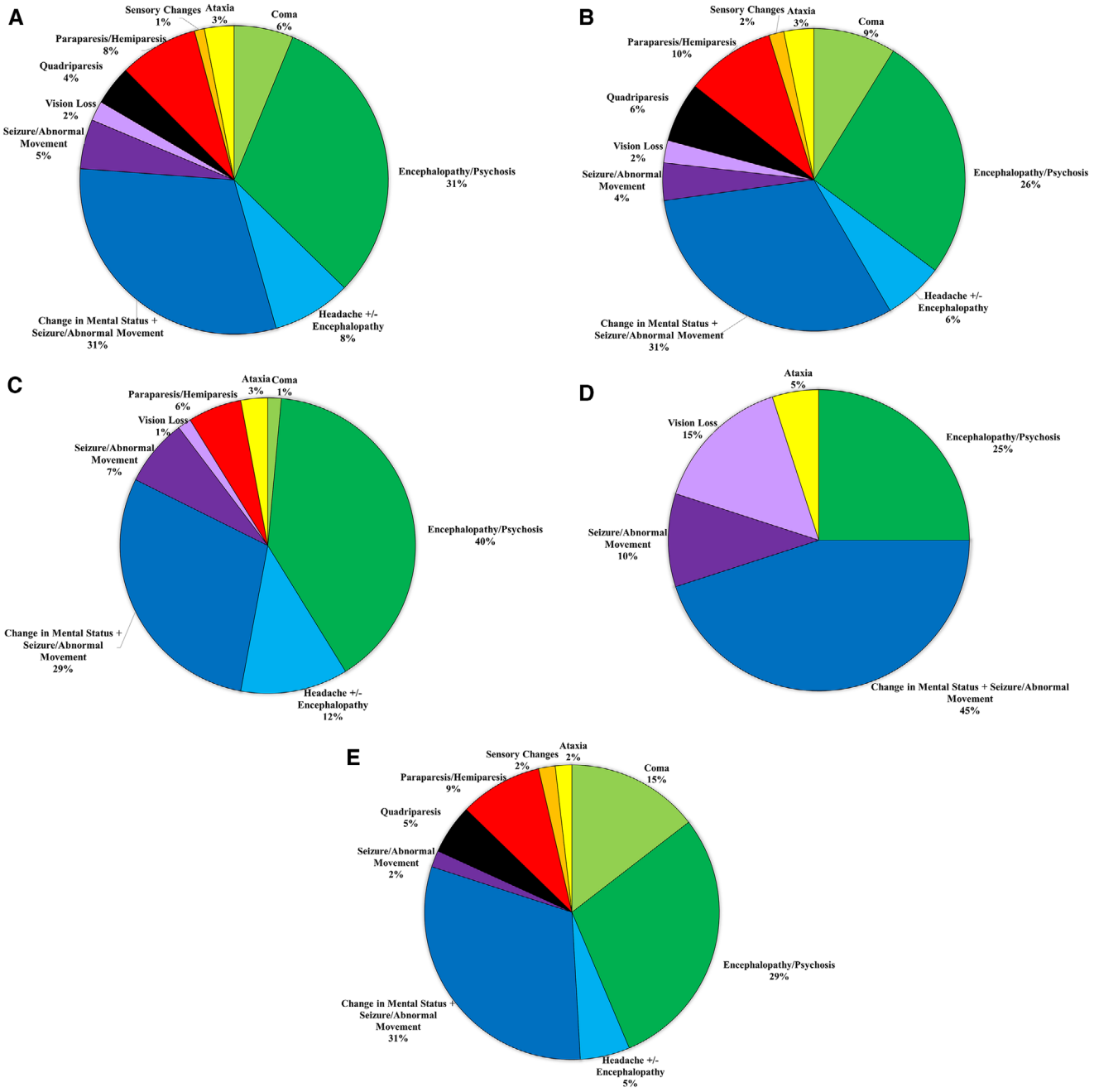


FIG 3 (A) Primary neurological symptoms prompting MRI and cerebrospinal fluid acquisition for all patients (193 patients); (B) primary neurological symptoms prompting MRI and cerebrospinal fluid acquisition for patients with central nervous system hyperintense lesions (125 patients); (C) primary neurological symptoms prompting MRI and cerebrospinal fluid acquisition for patients without central nervous system hyperintense lesions (68 patients); (D) primary neurological symptoms prompting MRI and cerebrospinal fluid acquisition for patients with leptomeningeal enhancement (20 patients); (E) primary neurological symptoms prompting MRI and cerebrospinal fluid acquisition for patients without leptomeningeal enhancement (55 patients)

patients with results from >1 MRI.[1,15–18,21,23–25,27,28,30,33,34,38,40,45,52–54,58,63,67–70,72–75,80,81,84,91,92,95,98,108,115,118,119,121,124] Additional details on MRI and CSF acquisition are in Table 1.

CSF findings

CSF WBC +/− red blood cell (RBC) count was reported for 186 (96%) patients; 61 (33%) had a CSF WBC count >5 cells/μl, a CSF WBC:RBC ratio >1:1000 or a CSF WBC count that was described as "increased."[1,2,10–28, 30–35,37–82,84,86,87,89–124] CSF protein was reported for 184 (95%) patients; 68 (37%) had a CSF protein >60 mg/dl or a CSF protein that was described as "increased."[1,2,10–28,30–35,37–46,49–75,77–82,84,86–124] There were 130 (67%) patients who had CSF SARS-CoV-2 PCR testing; nine (7%) were positive.[1,2,10–22,24,26–34,36–38,40,42,45,48–57,62,63,67,69–73,75–81,85,87,89,91–97,99–101,103–105,107,108,110,111,113–117,120–124] There were 102 (53%)

TABLE 1 MRI and cerebrospinal fluid acquisition

Characteristic	Central nervous system hyperintense lesions (125 patients)[1,2,10–96]	No central nervous system hyperintense lesions (68 patients)[1,2,54,79,81,82,96–124]	Leptomeningeal enhancement (20 patients)[2,28,29,37,55,56,61,62,82,84,92,93,96]	No leptomeningeal enhancement (55 patients)[1,10,12,14–17,20,22–24,26,27,30,33,34,36,38,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,96,102,103,105,111,117–119,121]
MRI acquisition				
Contrast utilized	51 (41%) [1,10,12,14–17,20,22–24,26–30,33,34,36–39,42,47,48,52–55,57,61,63,64,68,70,72–74,76,80,83,84,91,94,96]	19 (28%)[2,96,102,103,105,111,117–119,121]	20 (100%)[2,28,29,37,55,56,61,62,82,84,92,93,96]	55 (100%)[1,10,12,14–17,20,22–24,26,27,30,33,34,36,38,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,96,102,103,105,111,117–119,121]
Both MRI brain and MRI spine performed	33 (26%) [1,10–38]	3 (4%)[102,120,124]	3 (15%)[28,29,37]	18 (33%)[1,10,14–17,20,23,24,26,27,30,34,36,38]
Central nervous system hyperintense lesions on MRI brain only	12 (36%) [11,12,15,16,23,26,29,30]	0 (0%)	1 (33%) [29]	8 (44%)[15,16,23,26,30]
Central nervous system hyperintense lesions on MRI spine only	11 (33%) [1,10,13,17,20,21,24,25,27,31,32,34]	0 (0%)	0 (0%)	6 (33%) [1,10,17,20,24,27,34]
Central nervous system hyperintense lesions on MRI brain and MRI spine	10 (30%) [14,18,19,22,28,33,35–38]	0 (0%)	2 (66%) [28,37]	3 (17%)[14,36,38]
No central nervous system hyperintense lesions	0 (0%)	3 (100%) [102,120,124]	0 (0%)	1 (6%) [102]
Only MRI brain performed	88 (70%) [1,2,12,14,16,22,26,33,39–48,50–58,60–85,87,88,90–96]	65 (96%)[1,2,54,79,81,82,96–101,103–119,121–123]	17 (85%)[2,55,56,61,62,82,84,92,93,96]	37 (67%)[1,12,14,22,26,33,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,96,102,103,105,111,117–119,121]
Central nervous system hyperintense lesions present	88 (100%) [1,2,12,14,16,22,26,33,39–48,50–58,60–85,87,88,90–96]	0 (0%)	8 (40%) [55,56,61,62,84,92,93,96]	27 (73%)[1,12,14,22,26,33,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94]
Only MRI spine performed	4 (3%) [49,59,86,89]	0 (0%)	0 (0%)	0 (0%)
Central nervous system hyperintense lesions present	4 (100%) [49,59,86,89]	N/A	N/A	N/A
MRI image included in publication	97 (78%) [1,10–30,32–76,78,80,81,83,84,87–96]	6 (9%)[105,107,116,120–122]	11 (55%)[28,29,37,55,56,61,84,92,93,96]	44 (80%)[10,12,14–17,20,22–24,26,27,30,33,34,36,38,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,102,111,121]
>1 MRI brain/spine performed	29 (23%) [1,15–18,21,23,25,27,28,30,33,40,45,52,54,58,63,67,68,70,72,73,75,80,81,84,91,92,95]	5 (7%)[98,115,118,119,121,124]	4 (20%)[28,84,92,96]	16 (29%)[15–17,23,27,30,52,54,63,68,70,72,73,80,91,118,119,121]
Central nervous system hyperintense lesions improved	16 (55%) [16–18,28,40,45,52,54,58,63,68,70,72,73,91,92,95]	N/A	3 (75%) [28,92,96]	9 (60%)[16,17,52,54,63,68,70,72,73,91]
Central nervous system hyperintense lesions worsened	8 (28%) [1,21,23,27,30,67,80,84]	N/A	1 (33%) [84]	4 (27%)[23,27,30,80]
Central nervous system hyperintense lesions unchanged	5 (17%) [15,25,33,75,81]	N/A	0 (0%)	1 (7%) [15]

(Continues)

TABLE 1 (Continued)

Characteristic	Central nervous system hyperintense lesions (125 patients)[1,2,10–96]	No central nervous system hyperintense lesions (68 patients)[1,2,54,79,81,82,96–124]	Leptomeningeal enhancement (20 patients)[2,28,29,37,55,56,61,62,82,84,92,93,96]	No leptomeningeal enhancement (55 patients)[1,10,12,14–17,20,22–24,26,27,30,33,34,36,38,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,">96,102,103,105,111,117–119,121]
No central nervous system hyperintense lesions on either MRI	0 (0%)	N/A	0 (0%)	2 (13%)[118,119,121]
Leptomeningeal enhancement improved	N/A	N/A	2 (50%)[28,96]	N/A
Leptomeningeal enhancement worsened	N/A	N/A	2 (50%)[84,92]	N/A
CSF acquisition				
Number of days between MRI and lumbar puncture specified	30 (24%)[15,16,18,23,33,40,45,47,51,53,55,60,61,67,73,76–78,81,87,91–93]	11 (16%)[81,98,100–102,109,116,118,119,121]	4 (20%)[55,61,92,93]	15 (27%)[15,16,23,33,47,53,73,76,91,103,118,119,121]
Median number of days between MRI and lumbar puncture	0 (IQR −2 to 0)	0 (IQR −1 to 1)	0 (IQR −3 to 0)	0 (IQR −1 to 1)
CSF cell count/protein/SARS-CoV-2 polymerase chain reaction/antibody results from >1 lumbar puncture	12 (10%)[23,24,27,30,33,34,38,53,69,74,91,92,95]	5 (7%)[108,115,118,119,121,124]	1 (5%)[92]	10 (18%)[23,24,27,30,34,38,53,74,91,118,119,121]

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; N/A, not applicable.

patients who had CSF antibody, oligoclonal band, or immunoglobulin testing; 13 (13%) had evidence of possible intrathecal SARS-CoV-2 antibody synthesis, two of whom also had a positive CSF SARS-CoV-2 PCR.[1,2,11–14,16,20,22–34,37–39,42,46,53,54,56,57,61,64,67,70,72–74,79–82,86,87,92–96,104,107,108,115,118,119,121–124] Lastly, there were 41 (21%) patients who had CSF autoimmune antibody testing; three (7%) were positive.[1,16,22–24,33,34,38,53,54,57,62,67,72–74,77–79,81,82,87,91,94,95,100,104,107,108,111,115,118,119,121] Details on patients with a positive CSF SARS-CoV-2 PCR, possible intrathecal SARS-CoV-2 antibody synthesis, or autoimmune antibodies are in Table 2.

MRI findings

There were 134 patients (69%) with CNS hyperintense lesions and/or leptomeningeal enhancement.[1,2,10–96]

CNS hyperintense lesions

There were 125 patients with CNS hyperintense lesions and 68 patients without CNS hyperintense lesions.[1,2,10–124] Among the 125 patients with CNS hyperintense lesions, the most common lesion locations were the cortex (50, 40%), subcortical/deep white matter (44, 35%), and brainstem/cerebellum/spinal cord (37, 30%; Figure 4).[1,2,10–95] Of the 121 patients who had CNS hyperintense lesions on an MRI brain, 50 (41%) had multifocal hyperintense lesions.[1,2,10–48,50–58,60–85,87,88,90–95] Of the 29 patients with CNS hyperintense lesions who had >1 MRI brain/spine performed, 16 (55%) showed interval improvement on the follow-up MRI.[1,15–18,21,23,25,27,28,30,33,40,45,52,54,58,63,67,68,70,72,73,75,80,81,84,91,92,95]

Although there was no significant relationship between the presence of CNS hyperintense lesions and severity of COVID-19, patients with severe COVID-19 were significantly more likely to have hyperintense lesions in the subcortical/deep white matter and the corpus callosum than patients with mild/moderate COVID-19 (35% [27/77] vs. 16% [14/86], $p = 0.007$; and 21% [16/77] vs. 9% [8/86], $p = 0.047$, respectively). They were also significantly more likely to have multifocal CNS hyperintense lesions than patients with mild/moderate COVID-19 (57% [32/56] vs. 33% [13/40], $p = 0.001$).

Patients with coma/encephalopathy were less likely than patients with other neurological symptoms to have CNS hyperintense lesions in general (60% [90/150] vs. 81% [35/43], $p = 0.011$), and CNS hyperintense lesions in the brainstem/cerebellum/spinal cord or cranial nerve/cauda equina, in particular (19% [28/150] vs. 51% [20/39], $p<0.001$ and 0.7% [1/150] vs. 10% [4/39], $p = 0.007$, respectively). However, patients who were comatose/encephalopathic were significantly more likely to have CNS hyperintense lesions in the basal ganglia/thalami than patients with other neurological symptoms (15% [23/150] vs. 0% [0/39], $p = 0.005$).

Patients with CNS hyperintense lesions were significantly more likely to have a positive CSF SARS-CoV-2 PCR (10% [9/87] vs. 0%

TABLE 2 Patients with positive cerebrospinal fluid SARS-CoV-2 polymerase chain reaction (PCR), evidence of possible intrathecal SARS-CoV-2 antibody synthesis or autoimmune antibodies

Author	Age/sex	Severity of COVID-19	Neurological symptoms/signs	MRI findings	Days between MRI and lumbar puncture	Cerebrospinal fluid results	Outcome
Positive CSF SARS-CoV-2 PCR							
Demirci Otluoglu et al.[19]	48M	Moderate	• Headache • Anosmia	• Hyperintense lesions in the temporal lobe and cervical cord	N/A	• SARS-CoV-2 PCR positive (no Ct reported) • WBC 0 cells/μl • Protein 40 mg/dl • Glucose 90 mg/dl	Improved
Domingues et al.[20]	42F	Moderate	• Paresthesias of left hemibody	• Hyperintense lesion in the cervical cord • Normal MRI brain • No leptomeningeal enhancement	N/A	• SARS-CoV-2 PCR positive (no Ct reported) • Oligoclonal bands negative • WBC 1 cell/μl • Protein 32 mg/dl • Glucose 68 mg/dl	Improved
Fadakar et al.[62]	47M	Moderate	• Ataxia • Headache • Dysarthria • Nystagmus • Vertigo • Irregular rapid alternating movements	• Hyperintense lesions in the vermis and bilateral cerebellar hemispheres • Leptomeningeal enhancement in the cerebellum bilaterally	N/A	• SARS-CoV-2 PCR positive (Ct<35) • Autoimmune antibodies negative • WBC 10 cells/μl • Protein 58 mg/dl • Glucose 60 mg/dl	Improved
Kamal et al.[69]	31M	Mild	• Encephalopathy	• Hyperintense lesions in the frontal and anteromedial temporal lobes bilaterally	N/A	• SARS-CoV-2 PCR positive (no Ct reported) • WBC <5 cells/μl with RBC 150 cells/μl • Protein 45 mg/dl • Glucose 60 mg/dl	Improved
Moriguchi et al.[76]	24M	Mild	• Coma • Seizures • Headache	• Hyperintense lesions in right mesial temporal lobe and hippocampus • No leptomeningeal enhancement	−1	• SARS-CoV-2 PCR positive (Ct 37.12/37.52/36.44 for N1 gene and negative for N2) • WBC 12 cells/μl with RBC 0 cells/μl	No change after 15 days
Novi et al.[28]	64F	Moderate	• Vision loss • Right abdominal sensory level • Left lower extremity hyperreflexia • Headache • Anosmia • Ageusia	• Hyperintense lesions in the cortex, bilateral optic nerves, and thoracic cord • Leptomeningeal enhancement of optic nerves bilaterally	N/A	• SARS-CoV-2 PCR positive (no Ct reported) • Oligoclonal bands matched in serum • WBC 22 cells/μl • Protein 45 mg/dl	Improved

(Continues)

TABLE 2 (Continued)

Author	Age/sex	Severity of COVID-19	Neurological symptoms/signs	MRI findings	Days between MRI and lumbar puncture	Cerebrospinal fluid results	Outcome
Sattar et al.[87]	44M	Severe	• Encephalopathy • Seizure	• Hyperintense lesions in the bilateral frontal lobes	0	• SARS-CoV-2 PCR positive (no Ct reported) • Oligoclonal bands negative • IgG index normal • Autoimmune antibodies negative • WBC 11 cells/μl with RBC 1685 cells/μl • Protein 39 mg/dl • Glucose 75 mg/dl	Improved
Virhammar et al.[92]	55F	Mild	• Coma • Myoclonus	• Hyperintense lesions in bilateral thalami, medial temporal lobes, subinsula, and midbrain • Sulcal leptomeningeal enhancement	−3	• SARS-CoV-2 PCR negative x 2 then positive 1 week later with Ct 34.29 but negative on commercial assay and negative on repeat • IgG increased • Oligoclonal bands positive • Autoimmune antibodies negative • No pleocytosis • Protein increased • NfL and tau increased between second and fourth lumbar puncture • GFAp and IL6 were initially high but then decreased	Improved
Westhoff et al.[93]	69M	Moderate	• Seizures	• Hyperintense lesion in the right frontal lobe • Sulcal leptomeningeal enhancement	0	• SARS-CoV-2 PCR positive • Oligoclonal IgG synthesis 13.2 • WBC 1 cell/μl • Protein 110 mg/dl • Glucose 93 mg/dl	Improved
Possible intrathecal SARS-CoV-2 antibody synthesis							
Benameur et al.[14]	31F	Severe	• Coma	• Hyperintense lesions in the right frontal lobe and cervical cord • No leptomeningeal enhancement	N/A	• SARS-CoV-2 PCR negative • SARS-CoV-2 Ab positive with no further testing to distinguish intrathecal synthesis from transudation • WBC 115 cells/μl with RBC 7374 cells/μl • Protein >200 mg/dl • Glucose normal • IL-6, IL-8, IL-10, IP-10, and TNF-α increased • IL-1β normal	Death

(Continues)

TABLE 2 (Continued)

Author	Age/sex	Severity of COVID-19	Neurological symptoms/signs	MRI findings	Days between MRI and lumbar puncture	Cerebrospinal fluid results	Outcome
Benameur et al.[14]	34M	Severe	• Encephalopathy • Myoclonus	• Hyperintense lesion in the corpus callosum	N/A	• SARS-CoV-2 PCR negative • SARS-CoV-2 Ab positive with no further testing to distinguish intrathecal synthesis from transudation • WBC 1 cell/μl with RBC 29 cells/μl • Protein 37 mg/dl • IL-6, IL-8, IP-10, IL-1β, and TNF-α increased • IL-10 normal	N/A
Benameur et al.[14]	64M	Severe	• Encephalopathy • Myoclonus	• Hyperintense lesion in the right hippocampus • No leptomeningeal enhancement	N/A	• SARS-CoV-2 PCR negative • SARS-CoV-2 Ab positive with no further testing to distinguish intrathecal synthesis from transudation • WBC 0 cells/μl with RBC 7 cells/μl • Protein 21 mg/dl • Glucose mildly elevated • IL-6, IL-8, IL-10, IP-10, and TNF-α increased • IL-1β normal	Improved
Dogan et al.[96]	51F	Severe	• Encephalopathy	• Normal MRI brain • No leptomeningeal enhancement	N/A	• IgG index 0.78 (authors reported normal was <0.6) • IgG 3.23 mg/dl (authors reported normal was <3.4 mg/dl) • Oligoclonal bands negative • WBC 0 cells/μl • Protein 131 mg/dl • Glucose 120 mg/dl	Improved
Dono et al.[57]	81M	Moderate	• Coma • Seizures	• Hyperintense lesions in the bilateral parietal lobes, left temporal lobe, and right cingulate • No leptomeningeal enhancement	N/A	• SARS-CoV-2 PCR negative • Oligoclonal bands positive • Autoimmune antibodies negative • WBC 26 cells/μl • Protein 47 mg/dl • Glucose 78 mg/dl	Death

(Continues)

TABLE 2 (Continued)

Author	Age/sex	Severity of COVID-19	Neurological symptoms/signs	MRI findings	Days between MRI and lumbar puncture	Cerebrospinal fluid results	Outcome
Kremer et al.[2]	77F	Severe	• Encephalopathy • Pyramidal signs	• Diffuse leptomeningeal enhancement	N/A	• SARS-CoV-2 PCR negative • IgG 5.8 mg/dl (noted to be elevated but no normal value provided and no IgG index was provided to facilitate the distinction between intrathecal synthesis and transudation) • WBC 1 cell/μl • Protein 80 mg/dl • Glucose normal	N/A
Kremer et al.[2]	64M	Moderate	• Encephalopathy	• Hyperintense lesions in middle cerebellar peduncles	N/A	• SARS-CoV-2 PCR negative • IgG 5.6 mg/dl (noted to be elevated but no normal value provided and no IgG index was provided to facilitate the distinction between intrathecal synthesis and transudation) • WBC 40 cells/μl • Protein 110 mg/dl • Glucose normal	N/A
Noone et al.[79]	49M	Mild	• Encephalopathy	• Normal MRI brain	N/A	• SARS-CoV-2 PCR negative • "reactive to SARS-CoV-2 Ab" but no further information provided to facilitate the distinction between intrathecal synthesis and transudation • WBC normal • Protein 57 mg/dl	Improved
Palao et al.[29]	29F	Mild	• Vision loss • Anosmia • Dysgeusia	• Hyperintense lesions in the bilateral cortex, periventricular white matter, and right optic nerve • Enhancement of the right optic nerve	N/A	• SARS-CoV-2 PCR negative • Oligoclonal bands positive	Improved

(Continues)

TABLE 2 (Continued)

Author	Age/sex	Severity of COVID-19	Neurological symptoms/signs	MRI findings	Days between MRI and lumbar puncture	Cerebrospinal fluid results	Outcome
Rifino et al.[31]	66M	Mild	• Paraparesis • Decreased sensation • Hyperreflexia • Anosmia • Ageusia	• Hyperintense lesions in the cauda equina	N/A	• SARS-CoV-2 PCR negative • SARS-CoV-2 Ab positive but no further information provided to facilitate the distinction between intrathecal synthesis and transudation • WBC normal • Protein slightly increased	Improved
Positive CSF autoimmune antibodies							
Grimaldi et al.[107]	72M	Mild	• Ataxia • Tremor • Dysmetria • Dysarthria • Myoclonus	• Normal MRI brain	N/A	• SARS-CoV-2 PCR negative • Oligoclonal bands absent • Autoantibodies against Purkinje cell nuclei/striatal and hippocampal neurons • WBC 4 cells/μl • Protein 49 mg/dl	Improved
Guilmot et al.[108]	80N/A	Mild	• Encephalopathy • Seizures	• Normal MRI brain	N/A	• SARS-CoV-2 PCR negative • CSF-specific oligoclonal bands • Autoantibodies against Caspr2 • WBC 9 cells/μl	Improved
Monti et al.[115]	50M	Mild	• Encephalopathy • Seizures	• Normal MRI brain	N/A	• SARS-CoV-2 PCR negative • Oligoclonal bands matched • IgG index 0.67 initially then 1.45 1 month later • Autoantibodies against NMDA receptor positive • WBC 76 cells/μl then 16 cells/μl 1 month later • Protein 48 mg/dl then 105 mg/dl 3 weeks later • IL-6 and IL-8 elevated then increased 3 weeks later • IL-1β and TNF-α normal	

Abbreviations: Ab, antibody; Caspr2, contactin-associated protein 2; CSF, cerebrospinal fluid; Ct, cycle threshold; F, female; GFAp, glial fibrillary acidic protein; IgG, immunoglobulin; IL, interleukin; IP, interferon γ-induce protein; M, male; MRI, magnetic resonance imaging; NfL, neurofilament light chain; N/A, not available; NMDA, N-methyl-D-aspartic acid; PCR, polymerase chain reaction; RBC, red blood cells; TNF, tumor necrosis factor; WBC, white blood cells.

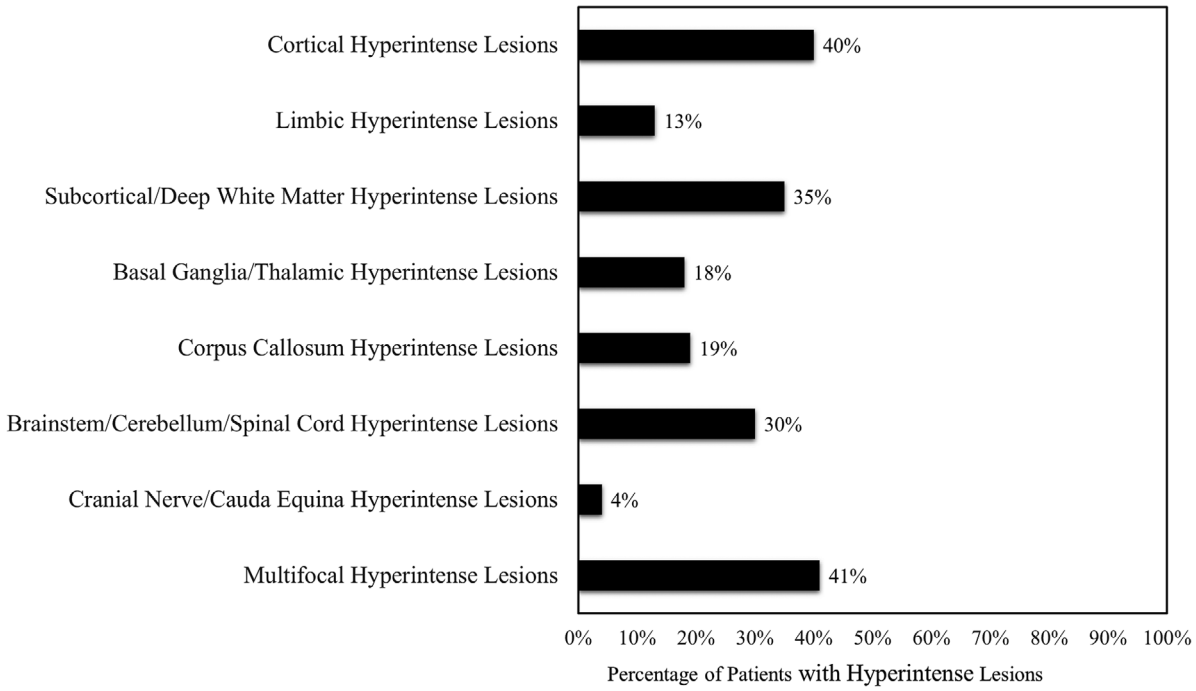


FIG 4 Location of hyperintense lesions (125 patients)

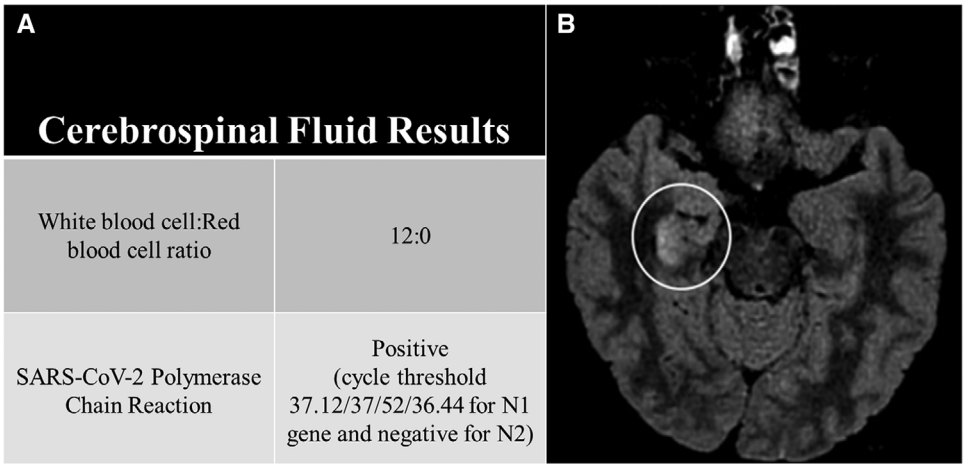
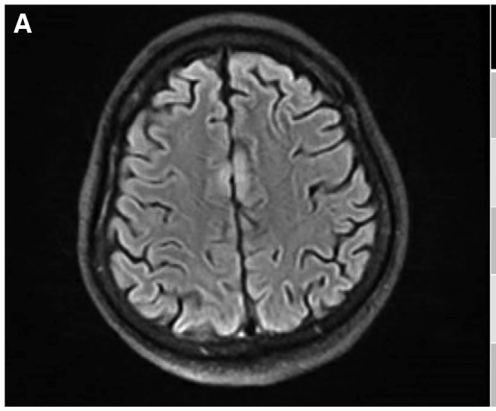


FIG 5 (A) Cerebrospinal fluid results;[76] (B) limbic hyperintense lesion in a patient with positive cerebrospinal fluid SARS-CoV-2 polymerase chain reaction (Reproduced with permission from Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with sars-coronavirus-2. Int J Infect Dis 2020;94:55-8)

[0/43], $p = 0.029$; Figures 5 and 6), particularly among patients with cortical hyperintense lesions (17% [5/30] vs. 4% [4/98], $p = 0.018$; Table 3). Patients with cranial nerve/cauda equina hyperintense lesions were significantly more likely to have evidence of possible intrathecal SARS-CoV-2 antibody synthesis (50% [2/4] vs. 11% [11/97], $p = 0.024$), but the presence of CNS hyperintense lesions in general, or in any other locations, and the number of CNS hyperintense lesions, did not significantly correlate with evidence of possible intrathecal SARS-CoV-2 antibody synthesis.

The presence of CNS hyperintense lesions did not significantly correlate with CSF protein >60 mg/dl or "increased," but patients with hyperintense lesions in the limbic system, basal ganglia/thalamus, or brainstem/cerebellum/spinal cord were significantly more likely to have CSF protein >60 mg/dl or "increased" than patients who did not have hyperintense lesions in these locations (64% [9/14] vs. 35% [58/166], $p = 0.042$; 62% [13/21] vs. 34% [54/159], $p = 0.013$; and 52% [24/46] vs. 32% [43/134], $p = 0.015$, respectively). Patients with multifocal CNS hyperintense lesions were also significantly more likely to



B

Cerebrospinal Fluid Results	
White blood cell:Red blood cell ratio	6:1000
Protein	39 mg/dL
SARS-CoV-2 Polymerase Chain Reaction	positive
Immunoglobulin G index	normal
Oligoclonal bands	negative

FIG 6 (A) Bifrontal cortical hyperintense lesions in a patient with positive cerebrospinal fluid SARS-CoV-2 polymerase chain reaction (Reproduced with permission from Sattar SBA, Sattar SBA, Haider MA, Zia Z, Niazi M, Iqbal QZ. Clinical, radiological, and molecular findings of acute encephalitis in a covid-19 patient: A rare case report. Cureus 2020;12:e10650); (B) cerebrospinal fluid results[87]

have CSF protein >60 mg/dl or "increased" than those with unifocal CNS hyperintense lesions (51% [23/45] vs. 30% [21/69], $p = 0.027$). Patients with CNS hyperintense lesions were significantly less likely to have CSF autoimmune antibodies (0% [0/29] vs. 25% [3/12], $p = 0.021$), but there was no significant difference in CSF autoimmune antibody results based on location or number of CNS hyperintense lesions.

There was no significant difference between pleocytosis based on presence, location, or number of CNS hyperintense lesions.

Leptomeningeal enhancement

Of 75 patients who had a contrast MRI, there were 20 (27%) patients with leptomeningeal enhancement; 12 (60%) had diffuse enhancement (Figures 7 and 8) and 8 (40%) had focal enhancement.[2,28,29,37,55,56,61,62,82,84,92,93,96] Patients with leptomeningeal enhancement were significantly less likely to have CNS hyperintense lesions than patients without leptomeningeal enhancement (55% [11/20] vs. 80% [44/55], $p = 0.03$). There was no significant relationship between the presence of leptomeningeal enhancement and location or number of CNS hyperintense lesions, severity of COVID-19, or coma/encephalopathy.

Patients with leptomeningeal enhancement were significantly more likely to have a positive CSF SARS-CoV-2 PCR (25% [4/16] vs. 5% [2/42], $p = 0.024$; Figure 9). Although the CSF SARS-CoV-2 PCR was positive for 44% (4/9) of patients with diffuse enhancement and 0% (0/7) of patients with focal enhancement, this difference was not statistically significant. Patients with leptomeningeal enhancement in general, and diffuse enhancement in particular, were nonsignificantly more likely to have evidence of possible intrathecal SARS-CoV-2 antibody synthesis (29% [4/14] vs. 17% [6/35], $p = 0.37$ and 43% [3/7] vs. 17% [1/6], $p = 0.56$, respectively). There was no significant difference between CSF WBC count, CSF protein, or CSF autoimmune antibodies based on the presence or location of enhancement.

DISCUSSION

Although numerous case series have demonstrated CNS hyperintense lesions and/or leptomeningeal enhancement may be seen on neuroimaging in patients with COVID-19 who have neurological symptoms, questions remain about the etiology for these findings.[1–6] In this meta-analysis of 193 patients with COVID-19 described in the literature who had an MRI brain and/or spine and CSF testing, we found a significant relationship between these neuroimaging findings and a positive CSF SARS-CoV-2 PCR.[1,2,10–124] These data may improve our understanding of the pathophysiology of these neuroimaging findings and guide decision-making about CSF testing in patients with COVID-19 who have neurological symptoms. Awareness of the MRI findings that can be seen in patients with evidence of SARS-CoV-2 in the CSF will also be important once the pandemic is over when COVID-19 is no longer part of the differential diagnosis for every patient, as there is a characteristic MRI phenotype associated with many viral encephalitides.[125] For example, herpes simplex virus-1 has a proclivity for the frontal and temporal lobes; Japanese encephalitis commonly involves the thalami and sometimes affects the basal ganglia, pons, midbrain, or cerebellum; varicella encephalitis causes cerebellar, thalamic, cortical or basal ganglia hyperintense lesions; and Parechovirus encephalitis affects the cerebral white matter and corpus callosum. Our results suggest that cortical hyperintense lesions and cranial nerve/cauda equina hyperintense lesions, in particular, are significantly associated with evidence of SARS-CoV-2 in the CSF, and that there is a trend toward increased likelihood of a positive CSF SARS-CoV-2 PCR in patients with diffuse leptomeningeal enhancement as compared with patients with focal leptomeningeal enhancement. However, in contrast with a recent study that showed leptomeningeal enhancement is common in patients with multiple sclerosis who have cortical or thalamic lesions, we found that patients with leptomeningeal enhancement were significantly less likely to have CNS hyperintense lesions.[126] It is not clear why a given virus has a particular signature of MRI findings. Although there is no specific treatment

TABLE 3 Comparison of cerebrospinal fluid results based on imaging findings

Imaging findings	CSF WBC count >5 cells/μl or "Increased" or CSF WBC:RBC ratio >1:1000	*p*-value	CSF protein>60 mg/dl or "Increased"	*p*-value	Positive CSF SARS-CoV-2 PCR	*p*-value	Antibody oroligoclonal band orimmunoglobulin results consistent with possible intrathecal SARS-CoV-2 antibody synthesis	*p*-value	CSF autoimmune antibodies	*p*-value
Central nervous system hyperintense lesions (125 patients) 1,2,10–96	34% (41/119)	0.63	38% (45/118)	0.75	10% (9/87)	0.029	15% (10/68)	0.54	0% (0/29)	0.02^
No central nervous system hyperintense lesions (68 patients) 1,2,54,79,81,82,96–124	30% (20/67)		35% (23/66)		0% (0/43)		9% (3/34)		25% (3/12)	
Cortical hyperintense lesions (50 patients) 1,14,16,19,22,23,26,28,29,33,39,41–44,47, 48,53–58,63–65,67,69,72,77,78,81–85,87, 93,96	33% (15/46)	0.97	42% (19/45)	0.42	17% (5/30)	0.02^	21% (5/24)	0.18	0% (0/10)	0.56
No cortical hyperintense lesions (139 patients*) 1,2,10–18,20–22,24–27,30–38,40,45,46,50, 51,54,60–62,66–68,70,71,73–76,79–82,88, 90–92,94–124	32% (44/136)		36% (48/135)		4% (4/98)		10% (8/77)		10% (3/31)	
Limbic hyperintense lesions (16 patients) 1,2,14,48,55,63,66,67,76,82,91,92,94	38% (6/16)	0.65	64% (9/14)	0.04^	15% (2/13)	0.21	29% (2/7)	0.2	0% (0/4)	1
No limbic hyperintense lesions (173 patients*) 1,2,10–47,50,51,53,54,56–58,60–62,64, 65,67–75,77–85,87,88,90,93,95–124	32% (53/166)		35% (58/166)		6% (7/115)		12% (11/94)		8% (3/37)	
Subcortical/deep white matter hyperintense lesions (44 patients) 1,2,12,15,16,18,22,23,26,30,33,36,38,45, 51,52,54,55,63,65,71,75,78–83,88,90,92,94,96	26% (10/39)	0.34	44% (18/41)	0.31	3% (1/34)	0.44	9% (2/23)	0.73	0% (0/12)	0.54
No subcortical/deep white matter hyperintense lesions (145 patients*) 1,2,10–14,16,17,19–22,24–28,31–35,37,39–44, 46–48,50,53,54,56–58,60–62,64,66–70,72–74, 76,77,81,82,84,85,87,91,93,95–124	34% (49/143)		35% (49/139)		9% (8/94)		14% (11/78)		10% (3/29)	

(Continues)

TABLE 3 (Continued)

Imaging findings	CSF WBC count >5 cells/μl or "Increased" or CSF WBC:RBC ratio >1:1000	*p*-value	CSF protein>60 mg/dl or "Increased"	*p*-value	Positive CSF SARS-CoV-2 PCR	*p*-value	Antibody oroligoclonal band orimmunoglobulin results consistent with possible intrathecal SARS-CoV-2 antibody synthesis	*p*-value	CSF autoimmune antibodies	*p*-value
Basal ganglia/thalamic hyperintense lesions (23 patients) 1,12,15,16,22,39,40,42,47,53,55,61,63, 70,75,82–84,88,92,94	38% (8/21)	0.56	62% (13/21)	0.01^	7% (1/15)	1	9% (1/11)	1	0% (0/3)	1
No basal ganglia/thalamic hyperintense lesions (166 patients*) 1,2,10–14,16–39,41,43–46,48,50,51, 54,56–58,60,62,64–69,71–74,76–82, 85,87,90,91,93,95–124	32% (51/161)		34% (54/159)		7% (8/113)		13% (12/90)		8% (3/38)	
Corpus callosum hyperintense lesions (24 patients) 1,2,11,14,15,18,22,26,38,46,50,51,55,60,68,71,73, 81,84	17% (4/24)	0.1	29% (7/24)	0.5	0% (0/18)	0.36	8% (1/12)	1	0% (0/5)	1
No corpus callosum hyperintense lesions (165 patients*) 1,2,10,12–14,16,17,19–37,40–45,47,48,53,54,56–58, 61–67,69–72,74–83,85,87,88,90–119	35% (55/158)		38% (60/156)		8% (9/110)		13% (12/89)		8% (3/36)	
Brainstem/cerebellum/ Spinal cord hyperintense lesions (37 patients) 1,2,10,12–14,16–28,32–39,42,43,47,49,51–53,55,59, 61–63,71,74,75,81,86,89,92,94	39% (18/46)	0.26	52% (24/46)	0.02^	14%>(5/37)	0.067	11% (3/28)	1	0% (0/11)	0.55
No brainstem/ cerebellum/spinal cord hyperintense lesions (152 patients) 1,2,11,12,14–16,22,26,29–31,33,40,41,44–46,48,50, 54,56–58,60,64–70,72,73,76–85, 87,88,90,91,93,95–124	30% (41/136)		32% (43/134)		4% (4/91)		14% (10/73)		10% (3/30)	
Cranial nerve/cauda equina hyperintense lesions (5 patients) 28,29,31,37,48	75% (3/4)	0.1	33% (1/3)	1	20% (1/5)	0.25	50% (2/4)	0.02^	N/A	N/A
No cranial nerve/cauda equina hyperintense lesions (188 patients) 1,2,10-27,30,32-36,38-47,49-51,53-124	31% (56/178)		37% (66/177)		7% (8/123)		11% (11/97)		7% (3/41)	

(Continues)

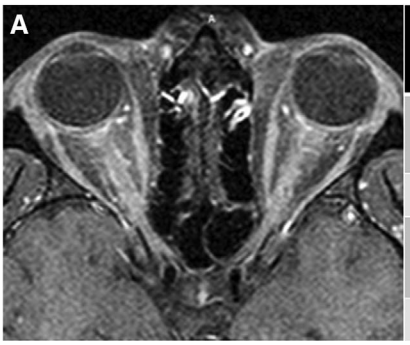
TABLE 3 (Continued)

Imaging findings	CSF WBC count >5 cells/μl or "Increased" or CSF WBC:RBC ratio >1:1000	*p*-value	CSF protein>60 mg/dl or "Increased"	*p*-value	Positive CSF SARS-CoV-2 PCR	*p*-value	Antibody oroligoclonal band orimmunoglobulin results consistent with possible intrathecal SARS-CoV-2 antibody synthesis	*p*-value	CSF autoimmune antibodies	*p*-value
Multifocal central nervous system hyperintense lesions (50 patients) 1,12,14–16,18,19,22,23,26,28,29,33,36,38,39,42,43,47,48,51–53,55,61,63,65,71,75,81–84,88,92,94,96	29% (13/45)	0.42	51% (23/45)	0.03^	9% (3/35)	0.73	11% (3/27)	0.73	0% (0/10)	N/A
Unifocal central nervous system hyperintense lesions (71 patients*) 1,2,10-14,16,17,20-22,24-27,30-35,37,40,41,44-46,50,54,56-58,60,62,64,66-70,72-74,76-82,85,87,90,91,93,95,96	37% (26/70)		30% (21/69)		14% (6/44)		18% (7/40)		0% (0/19)	
Leptomeningeal enhancement (20 patients) 2,28,29,37,55,56,61,62,82,84,92,93,96	37% (7/19)	1	44% (8/18)	1	25% (4/16)	0.02^	29% (4/14)	0.37	0% (0/1)	N/A
No leptomeningeal enhancement on contrast MRI (55 patients) 1,10,12,14–17,20,22–24,26,27,30,33,34,36,38,39,42,47,48,52–54,57,63,64,68,70,72–74,76,80,83,91,94,96,102,103,105,111,117–119,121	40% (21/53)		48% (24/50)		5% (2/42)		17% (6/35)		0% (0/18)	
Focal enhancement (8 patients) 2,29,61	29% (2/7)	0.66	33% (2/6)	0.64	0% (0/7)	0.088	17% (1/6)	0.56	N/A	N/A
Diffuse enhancement (12 patients) 2,28,37,55,56,62,82,84,92,93,96	42% (5/12)		50% (6/12)		44% (4/9)		43% (3/7)		0% (0/1)	

^:*p*-values that are statistically significant (<0.05).

*Includes only patients who had an MRI brain

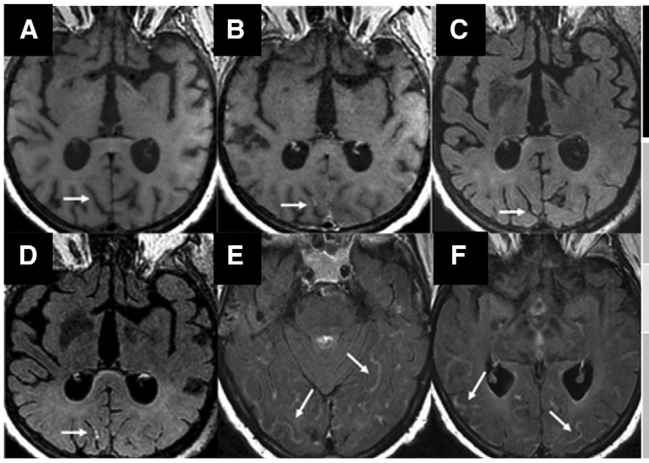
Abbreviations: CSF, cerebrospinal fluid; N/A, not applicable.



B

Cerebrospinal Fluid Results	
White blood cells	55 cells/μL
Protein	31 mg/dL
SARS-CoV-2 Polymerase Chain Reaction	Negative
Oligoclonal bands	Identical to serum

FIG 7 (A) Bilateral optic nerve enhancement in a patient with COVID-19 who had a negative cerebrospinal fluid SARS-CoV-2 polymerase chain reaction but a high titer (1:1000) cerebrospinal fluid myelin oligodendrocyte glycoprotein immunoglobulin G (Reproduced with permission from Zhou S, Jones-Lopez EC, Soneji DJ, Azevedo CJ, Patel VR. Myelin oligodendrocyte glycoprotein antibody-associated optic neuritis and myelitis in covid-19. J Neuroophthalmol 2020;40:398-402); (B) cerebrospinal fluid results[37]



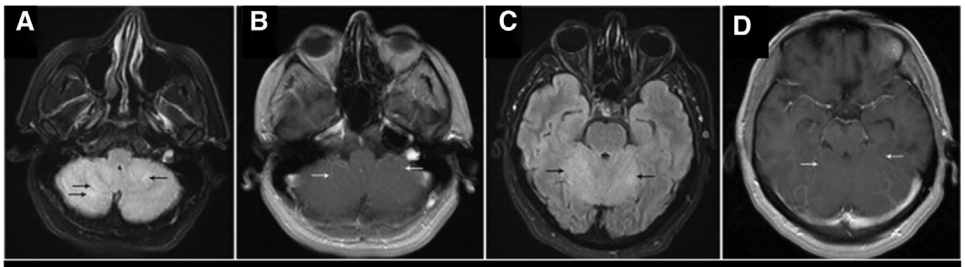
G

Cerebrospinal Fluid Results	
White blood cells	1 cell/μL
Protein	80 mg/dL
Immunoglobulin G	5.8 mg/dL

FIG 8 Diffuse leptomeningeal enhancement in a patient with COVID-19 who had a negative cerebrospinal fluid SARS-CoV-2 polymerase chain reaction but possible intrathecal SARS-CoV-2 antibody synthesis (elevated cerebrospinal fluid immunoglobulin G of 5.8 mg/dl): (A) axial T1 precontrast with no leptomeningeal signal (arrow); (B) axial T1 5-min after contrast shows focal leptomeningeal enhancement (arrow); (C) axial fluid-attenuated inversion recovery (FLAIR) precontrast with no leptomeningeal signal (arrow); (D) axial FLAIR immediately after contrast shows focal leptomeningeal enhancement (arrow); (E and F) axial FLAIR 10-min after contrast shows diffuse leptomeningeal enhancement (arrows). Reproduced with permission from Kremer S, Lersy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with covid-19: A retrospective multicenter study. Neurology 2020;95:e1868-e82; (G) cerebrospinal fluid results[2]

for patients with evidence of SARS-CoV-2 in the CSF at this time and data are limited to case reports and case series, our findings may also impact medical management and neuro-prognostication in the future. For example, among 19 patients with Bornavirus encephalitis, death occurred at a median of 22 (IQR 15–28) days following observation of CNS hyperintense lesions on MRI and a mean of 11 ± 8 days after development of basal ganglia hyperintense lesions.[127]

Because our results demonstrate that it is uncommon for patients with CNS hyperintense lesions or leptomeningeal enhancement to have a positive CSF SARS-CoV-2 PCR or evidence of possible intrathecal SARS-CoV-2 antibody synthesis, we suspect that these findings are usually attributable to processes other than viral neuroinvasion.[1,2,10–124] CNS hyperintense lesions may develop due to infection, ischemia, inflammation, toxic exposure, metabolic derangements, cancer, trauma, or genetic disorders.[128,129] Leptomeningeal enhancement is demonstrative of a breakdown in the blood–brain barrier due to infection (e.g., human T-lymphotropic virus or human immunodeficiency virus), inflammation (e.g., sarcoidosis or multiple sclerosis), acute stroke, or metastatic disease.[129,130] Absinta et al. also noted it was present in 8% (5/66) of healthy volunteers.[130] However, dural enhancement can also develop in the setting of intracranial hypotension following a lumbar puncture.[131] Systematic exploration of other etiologies for these findings was not feasible because detailed clinical data, including peak inflammatory markers and lowest oxygen saturation or partial pressure of oxygen, were not available to us. However, it is notable that there was a significant relationship between hyperproteinorrachia and the presence of CNS hyperintense lesions in the limbic system, basal ganglia/thalamus, and brainstem/cerebellum/spinal cord, and that patients with multifocal CNS hyperintense lesions had a higher protein than patients with



E

Cerebrospinal Fluid Results	
White blood cells	10 cells/μL
Protein	58 mg/dL
SARS-CoV-2 Polymerase Chain Reaction	positive

FIG 9 Leptomeningeal enhancement and cerebellar hyperintense lesions in a patient with COVID-19 who had a positive cerebrospinal fluid SARS-CoV-2 polymerase chain reaction: (A and C) axial fluid-attenuated inversion recovery imaging shows cerebellar hyperintense lesions (black arrows); (B and D) axial T1 postcontrast imaging shows cerebellar leptomeningeal enhancement (white arrows). Reproduced with permission from Fadakar N, Ghaemmaghami S, Masoompour SM, et al. A first case of acute cerebellitis associated with coronavirus disease (covid-19): A case report and literature review. Cerebellum 2020;19:911-4; (E) cerebrospinal fluid results[62]

unifocal CNS hyperintense lesions. Elevated CSF protein may be attributed to inflammation, ischemia, axonal injury, or infection.[132,133] It has also been associated with male sex, age, body mass index, endocrinopathies, neuropsychiatric disorders, uremia, and medications (such as phenytoin and phenothiazines).[134–137] Thus, we suspect that the CNS hyperintense lesions and leptomeningeal enhancement in our patients who did not have a positive CSF SARS-CoV-2 PCR or evidence of possible intrathecal SARS-CoV-2 antibody synthesis are the result of inflammation, hypoxia, or ischemia. Although we excluded patients with CNS hyperintense lesions that the authors of the case report/case series attributed to acute/chronic ischemia, this does not preclude the possibility that ischemia could be responsible for any of the included patients' neuroimaging findings. Similarly, while we excluded patients whose MRI findings were reported as only a diagnosis rather than described, such as "acute disseminated encephalomyelitis," this does not preclude the included patients (whose imaging findings were described) from having acute disseminated encephalomyelitis. Of course, in the absence of prior neuroimaging, the chronicity of these findings is unknown; in some cases, their development may have preceded the diagnosis of COVID-19.

We also found a significant relationship between the presence of CSF autoimmune antibodies and the absence of CNS hyperintense lesions; of the 41 patients who had CSF autoimmune antibody testing, all three patients who had positive results (autoantibodies against: Purkinje cell nuclei/striatal and hippocampal neurons, contactin-associated protein 2, and N-methyl-D-aspartic acid [NMDA]) had a normal MRI brain.[1,16,22–24,33,34,38,53,54,57,62,67,72–74,77–79,81,82,87,91,94,95,100,104,107,108,111,115,118,119,121]

Patients with autoimmune encephalitis, in general, have a normal MRI brain in ~33% of cases, but patients with NMDA encephalitis, in particular, have a normal MRI in 50–89% of cases.[138,139] Among patients with autoimmune encephalitis who have an abnormal MRI brain, CNS hyperintense lesions typically involve the limbic system, but can also be present in the cortex, subcortical/deep white matter, basal ganglia, thalami, cerebellum, brainstem, or spine.[139]

Our findings are limited by our methodology. Because patients were identified via review of the literature: we were unable to review all of the neuroimaging ourselves, which precluded us from confirming the findings described by the authors or performing a more nuanced assessment of the relationship between CSF findings and the appearance or location of CNS hyperintense lesions (such as a detailed parsed evaluation of cortical hyperintense lesions by subtype);[126] MRI technique, CSF test selection, and timing relative to neuroimaging were not standardized; CSF tests were performed at different laboratories; and some patients had more than one lumbar puncture and/or MRI, or did not have an MRI of both the brain and the spine. The MRI field strength, scanner model, sequence, resolution, and time between contrast injection and image acquisition can impact the evaluation for CNS hyperintense lesions or leptomeningeal enhancement.[2,140] CSF SARS-CoV-2 PCR results can be affected by contamination from shed airborne virus or blood, rapid CSF clearance, low viral load, genetic variability in the virus itself, and technical factors, including preanalytical error.[36,141–145] Similarly, the sensitivity and specificity among serological tests vary.[146,147] Although we conservatively considered all patients with evidence of possible intrathecal SARS-CoV-2 antibody synthesis based on the results of antibody, oligoclonal band, or immunoglobulin testing: (1) none of these patients had intrathecal and serum SARS-CoV-2 antibody titers reported; (2) evidence of intrathecal antibody synthesis based on oligoclonal band or immunoglobulin analysis is not definitively indicative of SARS-CoV-2 antibody

synthesis and could reflect intrathecal synthesis of other antibodies, such as antibodies to myelin or autoimmune antibodies; and (3) some of the patients with evidence of possible intrathecal SARS-CoV-2 antibody synthesis may, in fact, have had antibodies in the CSF as a result of transudation of antibodies, or the cells that secrete them, via a damaged blood–brain barrier or a traumatic tap, rather than intrathecal antibody synthesis.[14,107,108,115,148,149] Our statistical analysis was also impacted by the low number of patients with a positive CSF SARS-CoV-2 PCR, evidence of possible intrathecal SARS-CoV-2 antibody synthesis, and CSF autoimmune antibodies. Further, certain imaging findings (such as cranial nerve/cauda equina hyperintense lesions) were quite rare, which is notable given that it is believed that viruses may enter the CNS via cranial or peripheral nerves.[150–152] Although we found a correlation between a positive CSF SARS-CoV-2 PCR and both CNS hyperintense lesions and leptomeningeal enhancement, we cannot make deductions about causality; this is particularly relevant for patients with leptomeningeal enhancement, as while this finding can develop due to infection, it can also be indicative of breakdown in the blood–brain barrier due to inflammation, which would allow SARS-CoV-2 to enter the CSF.[129] It is also important to note that while CSF testing can be used to evaluate for viral neuroinvasion, this is not as definitive as neuropathology studies. Autopsy studies that correlate neuropathology findings with premorbid clinical and neuroimaging results are needed. Lastly, this review focuses on CSF findings in patients with COVID-19 who have CNS hyperintense lesions not attributed to acute/chronic ischemia or leptomeningeal enhancement, but a future area of study could be CSF findings in patients with COVID-19 who have vascular neuroimaging findings (such as ischemic stroke and microhemorrhages).[153–156]

CONCLUSION

Based on this meta-analysis of data obtained from 193 patients with COVID-19 described in the literature who had an MRI brain and/or spine and CSF testing as workup for neurologic symptoms, we found that the presence of CNS hyperintense lesions or leptomeningeal enhancement on neuroimaging is associated with increased likelihood of a positive CSF SARS-CoV-2 PCR. However, most patients with COVID-19 who have CNS hyperintense lesions or leptomeningeal enhancement do not have evidence of SARS-CoV-2 in the CSF, suggesting that these findings are the result of other processes, such as inflammation, hypoxia, or ischemia. The etiology for these imaging findings should be explored further via neuropathology studies.

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ORCID

Ariane Lewis https://orcid.org/0000-0002-0756-7320
Kara R. Melmed https://orcid.org/0000-0003-4084-8586

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