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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Increase in Ventricle Size and the Evolution of White Matter Changes on Serial Imaging in Critically Ill Patients with COVID-19

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Abstract

Background: Evolution of brain magnetic resonance imaging (MRI) findings in critically ill patients with coronavirus disease 2019 (COVID-19) is unknown.

Methods: We retrospectively reviewed 4530 critically ill patients with COVID-19 admitted to three tertiary care hospitals in New York City from March 1 to June 30, 2020 to identify patients who had more than one brain MRI. We reviewed the initial and final MRI for each patient to (1) measure the percent change in the bicaudate index and third ventricular diameter and (2) evaluate changes in the presence and severity of white matter changes.

Results: Twenty-one patients had two MRIs separated by a median of 22 [Interquartile range (IQR) 14–30] days. Ventricle size increased for 15 patients (71%) between scans [median bicaudate index 0.16 (IQR 0.126–0.181) initially and 0.167 (IQR 0.138–0.203) on final imaging ($p < 0.001$); median third ventricular diameter 6.9 mm (IQR 5.4–10.3) initially and 7.2 mm (IQR 6.4–10.8) on final imaging ($p < 0.001$)]. Every patient had white matter changes on the initial and final MRI; between images, they worsened for seven patients (33%) and improved for three (14%).

Conclusions: On serial imaging of critically ill patients with COVID-19, ventricle size frequently increased over several weeks. White matter changes were often unchanged, but in some cases they worsened or improved, demonstrating there is likely a spectrum of pathophysiological processes responsible for these changes.

Keywords: COVID-19, SARS-CoV-2, Leukoencephalopathy, Ventricle

Introduction

Patients with coronavirus disease-2019 (COVID-19) can have a wide range of neuroimaging findings including cerebrovascular complications (acute ischemic infarcts, cerebral venous thrombosis, microhemorrhages), perfusion abnormalities, white matter (WM) changes, basal ganglia lesions, cytotoxic lesions in the corpus callosum, posterior reversible encephalopathy syndrome (PRES), hypoxic ischemic changes, toxic–metabolic changes, and meningeal enhancement [1–6]. Although it has been suggested that brain atrophy may occur after critical illness, this has not been examined in critically ill patients with COVID-19 [7, 8]. However, WM changes in patients with COVID-19 have garnered a lot of attention [9–14]. The pathophysiology behind these findings and the relationship between them and clinical outcome is unclear at this time.

Assessment of the evolution of neuroimaging findings can enhance our understanding of underlying pathophysiology. MRI findings change over time in different ways depending on the underlying mechanism of injury; this has been described in critical illness [8], ischemic stroke

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[15], PRES [16–18], and demyelinating diseases [19]. Thus, serial evaluation of neuroimaging in patients with COVID-19 can allow for measurement of ventricle size over time and may help distinguish between ischemic, inflammatory, infectious, demyelinating, and toxic–metabolic etiologies for WM changes.

Here, we investigate serial brain magnetic resonance imaging (MRI) findings in critically ill COVID-19 patients to assess changes in ventricle size and determine whether WM changes worsen, stabilize, or improve over time.

Methods

Patient Identification

Between March 1, 2020, and June 30, 2020, there were 4530 patients with COVID-19 diagnosed via nasopharyngeal swab PCR admitted to three tertiary care hospitals of our academic medical center at the epicenter of the COVID-19 pandemic in New York City. Of these, 162 patients (4%) had an MRI brain performed after diagnosis of COVID-19 and 32 (0.7%) had more than one MRI brain performed prior to July 8, 2020. We performed a retrospective chart review on these 32 patients and excluded patients who did not have acute hypoxic respiratory failure requiring intubation ($n=5$), had serial imaging for malignancy ($n=4$), had < 5 days between initial and final imaging ($n=1$), or had brain surgery ($n=1$) leaving a study population of 21 critically ill COVID-19 patients (see Fig. 1).

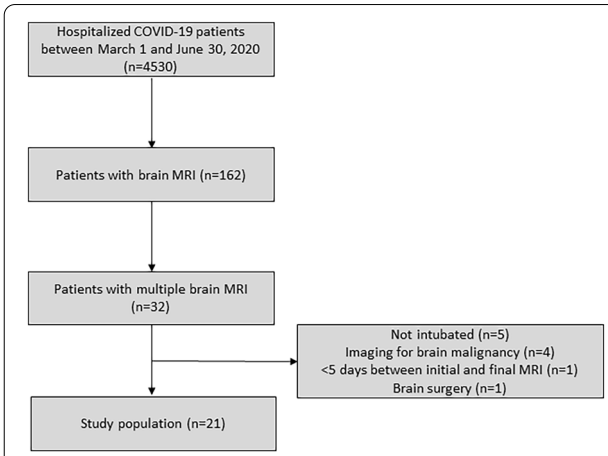

Fig. 1 Patient selection flowchart. This diagram illustrates the process by which we identified 21 patients for inclusion in this study from the 4530 patients hospitalized between March 1 and June 30, 2020, with COVID-19 at the three tertiary care hospitals of our academic medical center

Imaging Analysis

Two board-certified neurointensivists (Ariane Lewis and Kara Melmed) evaluated the initial and final MRIs for all 21 patients independently to (1) measure the bicaudate index and third ventricular diameter; (2) assess the presence, distribution and severity of WM changes; and (3) evaluate other pathology [20]. The evolution of ventricle size was calculated as percentage change of bicaudate index [(follow-up imaging − initial imaging)/initial imaging]*100 and third ventricular diameter between the initial and final MRI. The severity of WM lesions was quantified according to Fazekas score [21]; the presence of necrosis/cystic changes within these lesions was also noted. The initial MRI and final MRI were compared to evaluate subjective worsening, stability, or improvement of the WM changes over time. Discord in imaging evaluation was addressed via mutual review and adjudicated by a neuroradiologist (Rajan Jain).

Both the initial MRI and final MRI were performed using a 3.0 T MRI scanner for 16 patients (76%) and a 1.5 T MRI scanner for five patients (24%). MRIs performed on the 3.0 T scanner included susceptibility-weighted imaging (SWI), while those on the 1.5 T scanner included T2*-weighted gradient-recalled echo imaging (GRE).

Data Collection

Demographic, clinical, and laboratory data were collected for each patient for the time period from diagnosis of COVID-19 to the initial MRI and the time period between the initial MRI and the final MRI for each patient. Glasgow coma scale (GCS) score and modified Rankin scale (mRS) score were determined based on retrospective chart review by a board-certified neurointensivist (Ariane Lewis) of text included in clinician, nursing, and physical/occupational therapy notes.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics Version 25. Fisher's exact test, Mann–Whitney U test, and Spearman correlation were used, as appropriate. A p value < 0.05 was considered statistically significant. This study was approved by the NYU Grossman School of Medicine Institutional Review Board. Consent was waived due to the retrospective nature of the study.

Results

Of the 21 patients, the majority (18, 86%) were male and the median age was 63 years [Interquartile range (IQR) 50–69]. Most patients (16, 76%) had history of hypertension. Initial MRI and final MRI were done at a median of 25 (IQR 17–33) and 49 (IQR 39–60) days after admission, respectively, and were separated by a median of 22 (IQR 14–30) days. The indication for the initial MRI for nearly all patients (19, 91%) was encephalopathy. Similarly, the

indication for the final MRI was encephalopathy and/or the desire to follow-up on prior imaging for nearly all patients (19, 91%). Ventilator support was needed for a median of 21 (IQR 16–19) days before the first MRI and 20 (IQR 10–31) days between the first and final MRI. The median GCS score on the day of the initial MRI was 3 (IQR 3–6) and improved only slightly by the final MRI to 5 (IQR 3–6); the final GCS score, obtained at a median of 91 (IQR 64–101) days after admission, was 6 (IQR 6–12), and all patients had a final mRS score of 4–6 [4 (2, 10%); 5 (13, 62%); 6 (6, 29%)]. Other demographic, comorbidity, medication, vitals, laboratory, and in-hospital treatment and complication data are in Table 1.

Summary data on ventricle size and WM changes are in Table 2. Between the initial and final MRI, the bicaudate index and/or third ventricular diameter increased for 15 patients (71%), 2 (13%) of whom only had an increase in the bicaudate index and 2 (13%) of whom only had an increase in the third ventricular diameter (see Fig. 2a, b). The median time between MRIs was slightly longer for patients who had an increase in the bicaudate index and/or third ventricular diameter than those who did not, but this was not statistically significant [22 (IQR 14–45) days vs. 16 (IQR 10–33) days, $p = 0.424$]. There was an increase in the median bicaudate index and the median 3rd ventricular diameter between initial and final imaging [median bicaudate index 0.160 (IQR 0.126–0.181) mm on initial imaging and 0.167 (IQR 0.138–0.203) mm on final imaging ($p < 0.001$); median 3rd ventricular diameter 6.9 (IQR 5.4–10.3) mm on initial imaging and 7.2 (IQR 6.4–10.8) mm on final imaging ($p < 0.001$)]. The median percentage change between the initial and final imaging was 4.4% (IQR −3–20) for the bicaudate index and 4.1% (0–25) for the third ventricular diameter. There was no significant relationship between increase in ventricle size and ventilator days prior to the final MRI, need for dialysis, cardiac arrest, blood pressure, lowest PaO_2/FiO_2 ratio, inflammatory markers, worsening of WM changes, final GCS score or death (Table 3).

All 21 patients had WM changes on their initial MRI: 8 (38%) were Fazekas 1, 7 (33%) were Fazekas 2, and 6 (29%) patients were Fazekas 3. The percentage of patients with each Fazekas score was the same on follow-up imaging (though one patient went from Fazekas 2 to 3 and one went from Fazekas 3 to 2), but on subjective assessment of each patient's serial images, the WM changes for 7 patients (33%) worsened, 3 (14%) improved, and 11 (52%) were unchanged (Fig. 2). The median time between MRIs was slightly longer for patients who had worsening of WM changes than those who did not, but this was not statistically significant [25 (IQR 14–50) days vs. 21 (IQR 10–32) days, $p = 0.322$]. On the initial MRI, WM changes were predominantly periventricular (21, 100%), juxtacortical (17, 81%), and subcortical (17, 81%) and less commonly in the brainstem (6, 29%), precentral gyrus (6, 29%), or cerebellum (4, 19%). On follow-up imaging, WM changes were in the following regions: periventricular (21, 100%), subcortical (19, 91%), juxtacortical (17, 81%), brainstem (7, 33%), precentral gyrus (5, 24%), and cerebellum (4, 19%). Necrosis/cystic change was present in WM changes on initial imaging for seven (33%) patients and on follow-up imaging for ten (48%) patients. There was no significant relationship between worsening of WM changes and ventilator days prior to the final MRI, need for dialysis, cardiac arrest, blood pressure, lowest PaO_2/FiO_2 ratio, inflammatory markers, final GCS score or death (Table 3).

Imaging characteristics of individual patients are in Supplemental Table 1. In addition to increase in ventricle size and WM changes, the following findings were identified: microhemorrhages (18 patients; Fig. 3), ischemic stroke (5 patients), cortical ribboning (3 patients), hemorrhagic stroke (1 patient), subarachnoid and intraventricular hemorrhage (1 patient), and pachymeningeal enhancement (1 patient).

Discussion

There have been multiple reports describing neuroimaging in patients with COVID-19, but there has been no systematic study of ventricle size or WM changes over time [1–6, 9–14]. We describe the evolution of MRI brain findings in 21 critically ill patients with COVID-19 over the course of their hospitalization. After a period of only several weeks, over half of our patients (71%) developed increased bicaudate index and/or third ventricular diameter on serial scans. All patients had WM changes (the majority of which was stable on serial imaging, but some patients showed worsening WM changes and others showed improvement). In addition to these findings, most patients (86%) had microhemorrhages.

Although one case report noted hippocampal atrophy in a patient with COVID-19 [22], development of increased ventricle size over several weeks in critically ill patients with COVID-19 has not been widely described. Reports of serial brain imaging in critically ill patients with other diseases have demonstrated development of both global and focal atrophy [7, 8]. While our cohort was too small to demonstrate any statistically significant findings, we suspect that increase in ventricle size in critically ill patients with COVID-19 is likely the result of hypoxic injury. Relatedly, although there was no significant relationship between cardiac arrest and increase in ventricle size, this might be the result of our sample size, as MRI data from survivors of out-of-hospital cardiac arrest showed decreased regional grey matter volume compared to healthy controls [23]. Another factor that may

Table 1 Pre-hospitalization and hospitalization data

Demographics	*N* = 21	
Age, years, median (IQR)	63 (50–69)	
Male, *n* (%)	18 (86%)	
Race		
White, *n* (%)	8 (38%)	
Asian, *n* (%)	1 (5%)	
African-American, *n* (%)	2 (10%)	
Unknown, *n* (%)	10 (48%)	
Hispanic, *n* (%)	6 (35%)	
Comorbidities		
Anxiety/depression, *n* (%)	2 (10%)	
Cognitive impairment, *n* (%)	1 (5%)	
Coronary artery disease, *n* (%)	2 (10%)	
Chronic kidney disease, *n* (%)	3 (14%)	
Diabetes mellitus, *n* (%)	8 (38%)	
Hypertension, *n* (%)	16 (76%)	
Hyperlipidemia, *n* (%)	11 (52%)	
Stroke/transient ischemic attack, *n* (%)	2 (10%)	
Outpatient medications		
Anticoagulation, *n* (%)	3 (14%)	
Antiplatelet agent, *n* (%)	4 (19%)	
Statin, *n* (%)	8 (38%)	
Vitals/laboratories	**Before MRI 1**	**Between MRI 1 and Final MRI**
Highest systolic blood pressure (mm Hg), median (IQR)	179 (165–196)	170 (151–192)
Lowest systolic blood pressure, (mm Hg), median (IQR)	82 (71–90)	88 (75–98)
Lowest PaO_2/FiO_2, median (IQR)	92 (71–126)[a]	163 (121–210)[a]
Highest BUN (mg/dL), median (IQR)	109 (66–142)	74 (36–103)
Highest creatinine (mg/dL), median (IQR)	5.5 (2.4–8.8)	1.8 (0.9–4.9)
Highest glucose (mg/dL), median (IQR)	337 (259–434)	222 (189–271)
Lowest glucose (mg/dL), median (IQR)	74 (70–86)	84 (77–92)
Highest leukocyte count (10*3/uL), median (IQR)	23 (16–26)	17 (13–21)
Lowest leukocyte count (10*3/uL), median (IQR)	5.6 (4.8–6.6)	6.0 (4.1–8.3)
Lowest platelet count (10*3/uL), median (IQR)	117 (76–143)	136 (87–178)
Highest INR, median (IQR)	1.4 (1.3–1.8)	1.3 (1.2–1.6)
Highest D-Dimer (ng/mL), median (IQR)	4911 (2340–7307)[a]	1523 (1191–5970)[a]
Highest procalcitonin (ng/mL), median (IQR)	11.5 (4.6–26.8)	1.1 (0.4–2.5)
Highest ESR (mm/h), median (IQR)	111 (94–111)[b]	99 (89–118)[c]
Highest CRP (mg/L), median (IQR)	304 (204–377)	118 (67–213)
Highest ferritin (ng/mL), median (IQR)	4557 (2882–14,689)	2183 (1178–2877)
Highest IL-6 (pg/mL), median (IQR)	84 (33–134)[a]	16 (8.9–37.3)[d]
Highest troponin (ng/mL), median (IQR)	0.3 (0.1–1.3)	0.03 (0.02–0.53)[e]
In-hospital treatment/complications		
COVID-19 Treatment		
Azithromycin, *n* (%)	21 (100%)	
Convalescent plasma, *n* (%)	0 (0%)	
Hydroxychloroquine, *n* (%)	20 (95%)	
Lopinavir/ritonavir, *n* (%)	4 (19%)	
Tocilizumab, *n* (%)	11 (52%)	
Other investigational therapy, *n* (%)	2 (10%)	
Extracorporeal membrane oxygenation, *n* (%)	0 (0%)	0 (0%)

Table 1 (continued)

Vitals/laboratories	Before MRI 1	Between MRI 1 and Final MRI
Dialysis, *n* (%)	11 (52%)	7 (33%)
Insulin drip, *n* (%)	6 (29%)	1 (5%)
Treatment dose anticoagulation, *n* (%)	18 (86%)	17 (81%)
Vasopressor therapy, *n* (%)	19 (91%)	9 (43%)
Cardiac arrest, *n* (%)	6 (29%)	1 (5%)
Ventilator days, median (IQR)	21 (16–19)	20 (10–31)
Neurologic examination		
GCS score on the day of MRI, median (IQR)	3 (3–6)	5 (3–6)
GCS score 2 weeks after final MRI, median (IQR)[f]	6 (4–8)	
Final mRS score, (*n*, %)[g]	4 (2, 10%); 5 (13, 62%); 6 (6, 29%)	
Final GCS score for survivors, median (IQR)[g]	6 (6–12)	

COVID-19 coronavirus disease-2019, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *GCS* Glasgow coma scale, *IL-6* interleukin 6, *INR* international normalized ratio, *IQR* interquartile range, *MRI* magnetic resonance imaging, *mRS* modified Rankin scale

[a] $n=20$; [b] $n=18$; [c] $n=12$; [d] $n=6$; [e] $n=10$; [f] $n=16$; [g] $n=$ median time from admission until last examination = 91 days (IQR 64–101)

Table 2 Summary of serial imaging findings

Characteristic	MRI 1	MRI 2	Change between MRI 1 and MRI 2
Ventricle size			Bicaudate index median percentage change 4.38% (IQR −2.96–20.46) Third ventricular diameter median percentage change 4.05% (IQR 0–25.46)
Bicaudate index (mm), median (IQR)	0.16 (0.126–0.181)	0.167 (0.138–0.203)	
Third ventricular diameter (mm), median (IQR)	6.9 (5.4–10.3)	7.2 (6.4–10.8)	
White matter leukoencephalopathy, n (%)			Better—3 (14%) Worse—7 (33%) Same—11 (52%)
Severity	$N=21$	$N=21$	
Fazekas 1, *n* (%)	8 (38%)	8 (38%)	
Fazekas 2, *n* (%)	7 (33%)	7 (33%)	
Fazekas 3, *n* (%)	6 (29%)	6 (29%)	
Location			
Precentral gyrus	6 (29%)	5 (24%)	
Juxtacortical	17 (81%)	17 (81%)	
Subcortical	17 (81%)	19 (90.5%)	
Periventricular	21 (100%)	21 (100%)	
Cerebellum	4 (19%)	4 (19%)	
Brainstem	6 (29%)	7 (33%)	
Necrosis/cystic changes, *n* (%)	7 (33%)	10 (48%)	

IQR interquartile range, *MRI* magnetic resonance imaging

explain the increase in ventricle size is cytokine storming, as brain volume loss has been noted to correlate with procalcitonin, interleukin-6, and C-reactive protein [8, 24, 25]. While increase in ventricle size can be attributed to processes other than critical illness including normal aging, alcoholism, and neurodegenerative diseases, none would have resulted in progressive increase in ventricle size over a mere several weeks [24]. It has been noted that degree of brain volume loss correlates with duration of intensive care unit (ICU) delirium and cognitive performance 1 year after recovery from critical illness, but deficits in memory, executive functioning, and attention may improve over time in ICU survivors; thus, long-term studies of neurological outcomes for critically ill patients with COVID-19 are needed [7, 8].

Multiple reports have described the presence of WM changes in patients with COVID-19 [1–6, 9–13, 26].

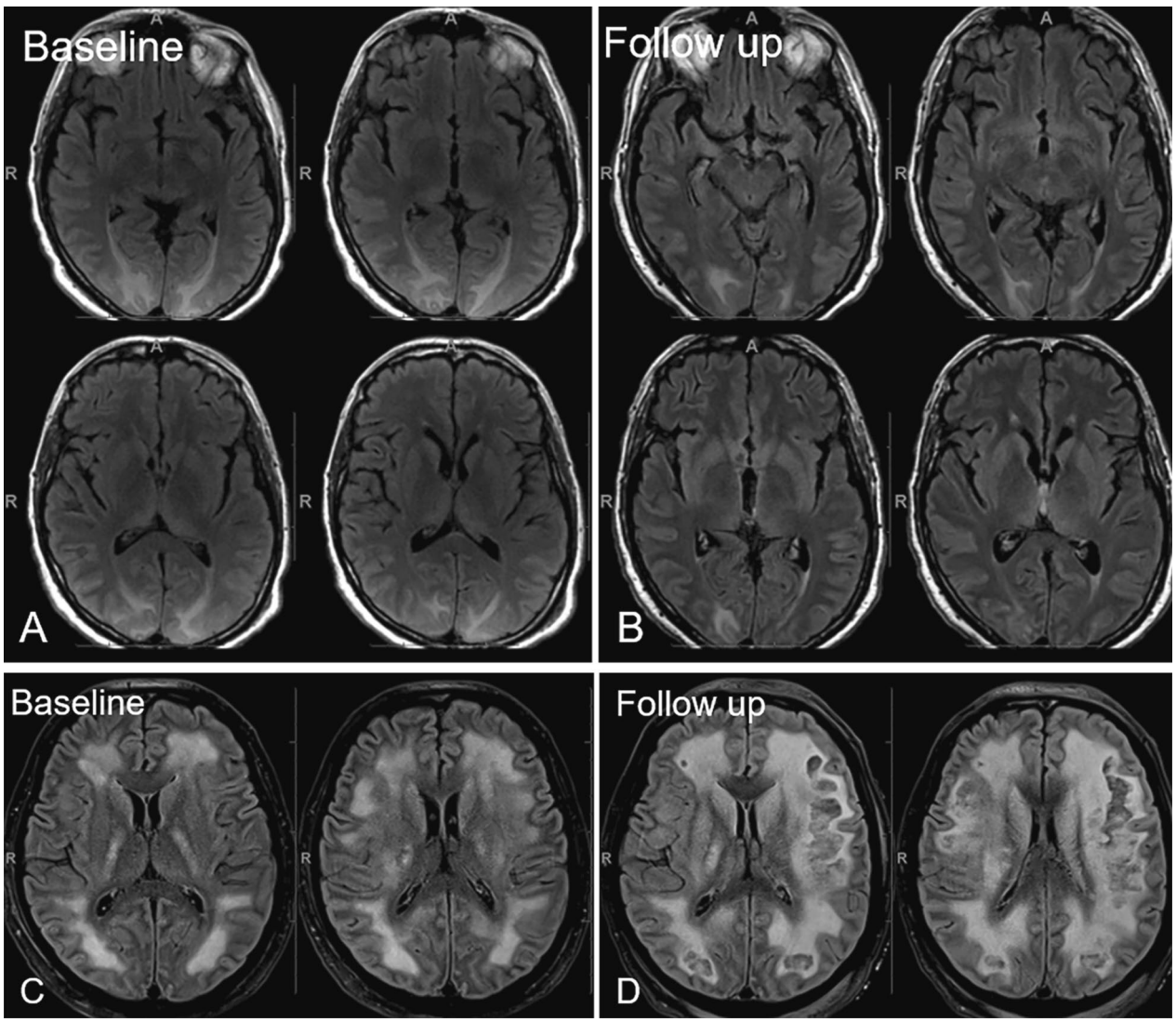

Fig. 2 White matter changes and increase in ventricle size from initial to final MRI. **a**, **b** Patient 6, a 61-year-old man with a history of hypertension, had an initial MRI **a** 17 days after admission and a final MRI **b** 24 days later. There were confluent posterior juxtacortical white matter changes present on the initial MRI which improved on the final MRI, consistent with posterior reversible encephalopathy syndrome. There was a notable increase in ventricular size between the MRIs (increase in the bicaudate index by 36.59% and in the third ventricular diameter by 44.64%). His course was complicated by a cardiac arrest with return of spontaneous circulation after 15 min prior to the initial MRI and renal failure requiring dialysis both prior to the initial MRI and between the initial and final MRI. He was ultimately declared brain dead following multifocal intracranial hemorrhage. **c**, **d** Patient 8, a 50-year-old man with a history of hypertension and diabetes (whose initial imaging was also described by Radmanesh et al. [12]) had an initial MRI **c** 21 days after admission and a final MRI **d** 11 days later. There were prominent symmetric confluent white matter changes present on the initial MRI which worsened on the final MRI and demonstrated progressive development of necrosis/cystic changes. His course was complicated by renal failure requiring dialysis prior to the initial MRI and a cardiac arrest with return of spontaneous circulation after 2.5 min between the initial and final MRI. He was discharged to a subacute rehab after 52 days with GCS score of 3 and mRS score of 5

However, we provide serial evaluations of WM changes over time and a formal scale to grade those changes. We found that approximately one-third of our patients were classified as having each Fazekas score on initial imaging. The majority of patients had stable WM changes on serial imaging, but, in some cases, WM changes worsened, and in others, they improved; notably, the Fazekas score only changed for two patients between the initial MRI and final MRI, despite the fact that seven patients (33%) had worsening of WM changes on subjective assessment and three (14%) had improvement in WM changes on subjective assessment. A number of mechanisms for WM

Table 3 Increase in ventricle size and worsening of white matter changes

Characteristic	Increase in ventricle size between MRI 1 and final MRI ($n=15$)	No increase in ventricle size between MRI 1 and final MRI ($n=6$)	*p* value	Worsening of white matter changes between MRI 1 and final MRI ($n=7$)	Improvement or no change in white matter changes between MRI 1 and final MRI ($n=14$)	*p* value
Treatment/complications before final MRI						
Days between MRIs, median (IQR)	22 (14–45)	16 (10–33)	0.424	25 (14–50)	21 (10–32)	0.322
Ventilator days, median (IQR)	42 (37–49)	43 (27–53)	0.85	42 (36–51)	42 (35–52)	0.856
Dialysis, *n* (%)	8 (53%)	3 (50%)	1	4 (57%)	7 (50%)	1
Cardiac arrest, *n* (%)	4 (27%)	3 (50%)	0.354	3 (43%)	4 (29%)	0.638
Vitals/laboratories before final MRI						
Highest systolic blood pressure (mm Hg), median (IQR)	176 (167–201)	195 (179–229)	0.791	179 (172–210)	187 (171–206)	0.689
Lowest systolic blood pressure (mm Hg), median (IQR)	83 (71–91)	71 (58–78)	0.154	64 (58–87)	80 (71–86)	0.743
Lowest PaO_2/FiO_2, median (IQR)	95 (70–126)	80 (64–137)	0.622	122 (77–180)	77 (66–110)	0.149
Highest procalcitonin (ng/mL), median (IQR)	8 (4.6–91.6)	13 (2.6–125)	0.91	6.4 (0.3–120)	12.7 (5.7–63.5)	0.636
Highest CRP (mg/L), median (IQR)	316 (202–396)	322 (244–392)	0.791	333 (189 –396)	314 (239–392)	0.689
Highest IL-6 (pg/mL), median (IQR)	99 (31–164)	66 (35–168)	0.91	38 (12–84)	112 (36–191)	0.094
Highest ferritin (ng/mL), median (IQR)	7169 (3664–21,255)	4161 (2421–5816)	0.154	4330 (2443–14,813)	4761 (3955–20,432)	0.488
Imaging changes						
White matter changes worsened, *n* (%)	5 (33%)	2 (33%)	1	–	–	–
Outcome						
Final GCS score for survivors, median (IQR)	6 (6–15)	8 (4–14)	1	6 (3–15)	7 (6–14)	0.281
Death, *n* (%)	4 (27%)	2 (33%)	1	0 (0%)	6 (43%)	0.61

CRP C-reactive protein, *GCS* Glasgow coma scale, *IL-6* interleukin 6, *IQR* interquartile range, *MRI* magnetic resonance imaging

changes in critically ill patients with COVID-19 have been postulated including hypoxia, infection, ischemia, demyelination, toxic-metabolic changes, and inflammation [9, 13, 14, 26]. In some cases, due to the symmetric appearance and posterior predominance of WM changes, these findings have been called PRES and have been attributed to breakdown of the blood–brain barrier from SARS-CoV-2 uptake into the central nervous system or blood pressure dysregulation [2, 27, 28]. PRES is generally associated with imaging resolution after 6 weeks [16]. Although our final MRI was performed 1–9 weeks after the initial MRI, the fact that only a minority of patients showed interval improvement argues against PRES as a common underlying mechanism for WM changes in COVID-19. For the one-third of patients whose WM changes worsened between the initial and final scan, the underlying pathology is uncertain and may be dynamic and variable. Our cohort was too small to identify any statistically significant factors associated with worsening of WM changes, and we did not evaluate the relationship between trends in vital signs or laboratory results and WM changes over time; further evaluation into factors associated with worsening of WM changes over time is needed. As half of the patients had stable WM changes

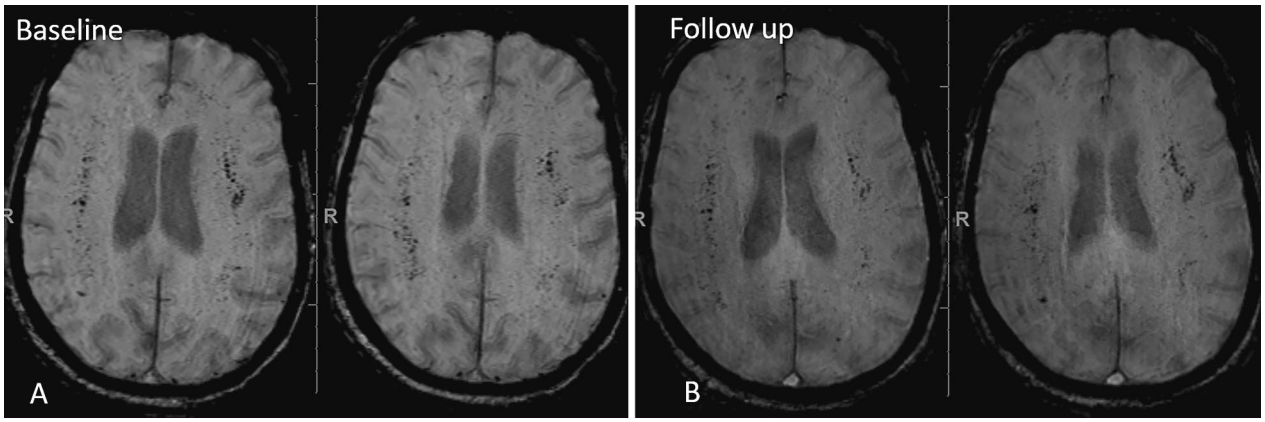

Fig. 3 Large number of microhemorrhages on serial imaging. Patient 16, a 72-year-old man with a history of hypertension and hyperlipidemia, had an initial MRI 42 days after admission and a final MRI 7 days later. There were many bilateral globi pallidi and centrum semiovale microhemorrhages in a watershed distribution on both the initial and final MRI. His course was complicated by renal failure requiring dialysis prior to the initial MRI. He was on a heparin drip for 15 days prior to the initial MRI (started empirically for elevated D-Dimer), but this was stopped because of thrombocytopenia (lowest platelet count was 28,000/ul before the initial MRI and 50,000/ul between the initial and final MRI). Highest systolic blood pressure was 190 mm Hg prior to the initial MRI and 140 mm Hg between the initial and final MRI. His highest INR was 1.4 before the initial MRI and 1.1 between the initial and final MRI. Highest D-Dimer was 2527 ng/mL before the initial MRI and 1350 ng/mL between the initial and final MRI. He had a cardiopulmonary arrest 95 days after admission and died

on serial imaging, their WM changes could be attributable to a static process related to critical illness or COVID-19 which occurred prior to the initial MRI [8]. Of course, as has been suggested elsewhere, it is feasible that some of these changes (particularly in patients who were Fazekas 1) are age-related and preceded COVID-19 [14].

There have also been a number of reports of microhemorrhages in critically ill patients with COVID-19 [1, 2, 9, 13, 29]. These findings have been attributed to consumption coagulopathy leading to medullary vein thrombosis or thrombotic microangiopathy, anticoagulation, hypoxemia, and endothelial injury [1, 9, 13, 29]. In contrast to the deep microhemorrhages associated with hypertension or the cortical microhemorrhages associated with amyloid angiopathy, the microhemorrhages associated with COVID-19 are diffuse and involve the cortex, subcortex, and brainstem with a unique predilection for the corpus callosum [9, 13]. These findings have been likened to changes seen in acute respiratory distress syndrome (ARDS), Susac's syndrome, thrombotic thrombocytopenic purpura, H1N1 influenza, high-altitude sickness, and cerebral malaria [2, 9, 13, 30–32]. Nearly all of the patients included in this study had microhemorrhages. It remains unclear whether microhemorrhages are related to critical illness in general, or COVID-19 in particular [29]. Further, it is worth noting that it may actually be a misnomer to refer to SWI/GRE changes as "microhemorrhages," because they may not have hemorrhagic components on histopathology; autopsy results will provide additional information about this in the future [13, 33, 34].

Limitations of our study include the fact that (1) it was retrospective; (2) the sample size was relatively small; (3) we did not have baseline neuroimaging prior to onset of COVID-19; (4) the time interval from admission to first MRI and between first and final MRI was not standardized; and (5) we were unable to compare our findings to control data from critically ill patients without COVID-19 who had serial MRIs. It is also worth noting that retrospective abstraction of GCS and mRS scores based on review of textual documentation in the medical record has not been validated. Nonetheless, this study adds to our understanding of neuroimaging changes in critically ill patients with COVID-19. While serial neuroimaging can teach us about increase in ventricle size and the evolution of WM changes in critically ill patients with COVID-19 and thereby improve awareness of the mechanisms responsible for these changes, neuropathology studies in patients with these findings are needed.

Conclusion

On serial imaging of critically ill patients with COVID-19, ventricle size frequently increased over a few weeks. The varied evolution of WM changes in this patient population suggests they are the result of both static and dynamic processes and that while some WM changes are reversible, others are irreversible. We suspect there is a spectrum of pathophysiological processes responsible for these MRI brain changes. Further studies with long-term

neurological assessments, serial neuroimaging, and histopathology are needed.

Supplementary Information
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Author's Contributions
SA was responsible for data collection, data analysis, drafting of the manuscript and approval of the final manuscript. KM, RJ and JC were responsible for study conception and design, data collection, critical revision of the manuscript and approval of the final manuscript. SD was responsible for data collection, critical revision of the manuscript and approval of the final manuscript. SG was responsible for study conception and design, critical revision of the manuscript and approval of the final manuscript. AL was responsible for study conception and design, data collection, data analysis, critical revision of the manuscript, supervision and approval of the final manuscript.

Source of Support
None.

Data Availability

Data collected for this study will be made available via e-mail request to the corresponding author.

Conflict of interest
All authors report no disclosures.

Ethical Approval/Informed Consent
This study was approved by the NYU Grossman School of Medicine Institutional Review Board. Consent was waived due to the retrospective nature of the study.

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