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Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection

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Summary

Of patients in the intensive care unit with COVID-19 infection who had neurologic symptoms and MRI, 44% (12/27) of patients had abnormal MRI findings.

A novel coronavirus, SARS-CoV-2, has caused an outbreak of severe pneumonia (COVID-19) in China that rapidly spread around the globe. Recent evidence highlights a relatively high percentage (36%) of central nervous system symptoms including headache, altered mental status, acute cerebrovascular disease and epilepsy in patients with COVID-19 (1). The rate of neurological symptoms is higher in patients with more severe respiratory disease status (1). The relatively high percentage of neurologic symptoms is concordant with studies showing neurotropism of coronavirus (2).

The current literature is limited regarding neuroimaging findings of patients with COVID-19 including acute hemorrhagic necrotizing encephalopathy and meningoencephalitis (3-5). The purpose of this study was to describe brain MRI findings in the evaluation of patients in the intensive care unit with COVID-19 pneumonia.

Materials and Methods

Local institutional review board approval was obtained for this retrospective study for patients evaluated from between March 1 and April 18, 2020. The requirement for informed consent was waived. The clinical course, neurological findings, laboratory data (including CSF analysis) and neuroimaging findings were retrospectively reviewed using a structured research form.

Indications and timing for brain MRI in patients with mechanic ventilation was decided on a protocol established by ICU teams. Full details are in the supplement at the end of this article (Appendix E1). MRIs were initially analyzed by institution's own neuroradiologists. Subsequently, all images were reviewed by two neuroradiologists (A.D., 29 years of experience in neuroradiology and N.K., 29 years of experience in neuroradiology) in consensus.

Results

Of 749 inpatients with COVID-19 infection at eight hospitals (2 university, 6 university affiliated hospitals), 235 patients (31%) required intensive care unit (ICU) admission during hospitalization. Fifty of 235 ICU patients (21%, 95%CI 16-27%) developed neurological symptoms.

Brain MRI was performed in 27/50 (54%) patients with neurologic symptoms (Fig 1). The median age of patients with MRI was 63 years (range 34-87 years, 21 males) (Table). 12/27 (44%, 95%CI 25-65%) patients who had MRI had acute findings. In 10/27 (37%) patients, cortical FLAIR signal abnormality (Fig 2; Appendix E1, Figs E1-E4) was present. Accompanying subcortical and deep white matter signal abnormality on FLAIR images were each present in 3 patients. Abnormalities involved the frontal lobe in 4, parietal lobe in 3, occipital lobe in 4, temporal lobe in 1, insular cortex in 3 and cingulate gyrus in 3 patients.

Cerobrospinal fluid (CSF) was obtained in 5 out of 10 patients with cortical signal abnormalities. Total protein was elevated (mean 79.9 mg/dL, range 59.9 – 109.7 mg/dL) in 4 of these patients. The cell count, glucose levels, IgG index, albumin were within normal limits, and RT-PCR for HSV DNA and SARS-CoV-2 were negative in all 5 specimens. Oligoclonal bands were checked in 3 specimens and were negative.

Other acute intracranial findings in the absence of cortical signal abnormality included 1 patient with acute transverse sinus thrombosis and 1 patient with acute infarction in right middle cerebral artery territory.

In 15/27 cases (56%), MR did not reveal any COVID-19 related or acute intracranial findings. CSF was obtained in two of these cases which showed elevated CSF protein (mean 98 mg/dL) despite negative MRI. A full description of MRI findings is in the supplement at the

end of this article (Appendix E1).

Discussion

Current evidence suggests an association of neurologic manifestations with COVID-19 infection including acute stroke (6%) and altered mental status (15%) (1). Neurotropism of coronavirus may account for the relatively high percentage of neurologic involvement (6, 7). In addition to neurotropism, another potential mechanism for neurologic manifestations might be related to cytokine storm syndrome (8). In addition to findings of encephalitis, increased thrombosis rates in coronavirus infection has been reported. In patients with SARS-CoV, increased incidence of deep venous thrombosis and pulmonary embolism was observed despite optimal anticoagulant therapy (9). Additionally, intracranial arterial stroke cases have been reported in SARS patients receiving IVIG treatment (9).

A recent series from France reported 84% neurologic signs in 58 COVID-19 patients admitted to ICU. Out of the 13 cranial MRIs performed, leptomeningeal enhancement was noted in 8 cases (5). In our series, the most common imaging finding was cortical signal abnormalities on FLAIR images 10/27 (37%), accompanied by cortical diffusion restriction, leptomeningeal enhancement or cortical blooming artifact in some of these cases. The main differential diagnosis for this constellation of findings is infectious or autoimmune encephalitis, seizure, hypoglycemia and hypoxia. (10-16) The cases with bilateral frontal involvement may have hypoxia as underlying pathogenesis given the underlying respiratory distress and frontotemporal hypoperfusion as demonstrated by Helms et al., in COVID-19 patients admitted to ICU (5). Cortical microhemorrhages and breakdown of blood-brain barrier can accompany hypoxia which can result in such an imaging pattern. Postictal state is also a plausible etiology for our imaging findings, however the relative symmetry and deep white matter involvement in our cases don't

support postictal changes. Hypoglycemia can act as a potential mimicker, however no episode of hypoglycemia occurred during the ICU course of patients. COVID-19 with its neurotropic potential may result in infectious or autoimmune encephalitis (3, 4). Certain viral and autoimmune encephalitis can have specific pattern of involvement that is helpful to establish a differential list, however nonspecific imaging pattern in our series hinders achieving a specific diagnosis based on MRI (10). In addition, the complex clinical course including comorbid conditions like diabetes mellitus, long ICU stay with multidrug regimens, respiratory distress with hypoxia episodes can all act as confounding factors and a clear cause-effect relationship between COVID-19 infection and MRI findings is hard to establish in the absence of more specific CSF findings. More data is needed to determine which imaging findings are related to neurotropism of COVID-19 and which are related to other etiologies like cytokine storm syndrome, hypoxia, subclinical seizures and critical illness–related encephalopathy.

Limitations of the current study are the retrospective and multicenter nature of the study, lack of standardization of indications across hospitals.

This report may help increase awareness for possible neurological involvement of SARS-CoV-2 for patients in the ICU and especially for patients who do not tolerate extubation despite improvement of respiratory findings.

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Table. Demographic and clinical features of patients with COVID-19 infection in the intensive care unit with cranial MRI

Characteristic	All ICU patients with cranial MRI (n, %) n=27	Abnormal brain MRI (n, %) n=12	Normal brain MRI (n, %) n=15
Age (years)*	63 (34-87)	62 (34-87)	63 (51-77)
Males	21 (78%)	11 (92%)	10 (67%)
Comorbidities	16 HT, 11 DM, 2 CVA, 3 CAD, 1 AF, 2 CHF, 4 CKD, 1 lung cancer, 1 Addison's disease	6 HT, 5 DM, 1 CAD, 1 AF, 1 CKD, 1 Addison's disease	10 HT, 6 DM, 2 CVA, 2 CAD, 2 CHF, 3 CKD, 1 lung cancer
Symptom onset to ICU admission*	3 days (0-20)	3 days (0-20)	4 days (0-14)
Intubation/ noninvasive ventilator support	19/8	9/3	10/5
CSF analysis	7 (26%)	5 (42%)	2 (13%)
ICU admission to MRI examination*	7 days (0-24)	4 with increased protein without pleocystosis 8 days (0-16)	2 with increased protein without pleocystosis 4 days (0-24)

*The time intervals and age of the patients are presented as median (minimum-maximum).

AF: atrial fibrillation, CAD: coronary artery disease, CKD: chronic kidney disease, CVA: cerebrovascular accident, DM: diabetes mellitus, HT: hypertension.

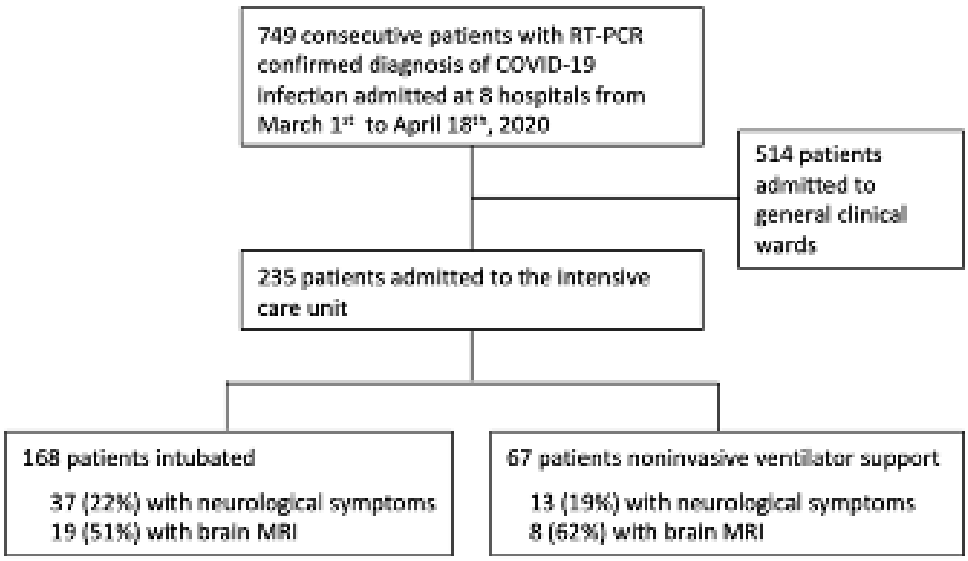

Figure 1: Flowchart for patient inclusion.

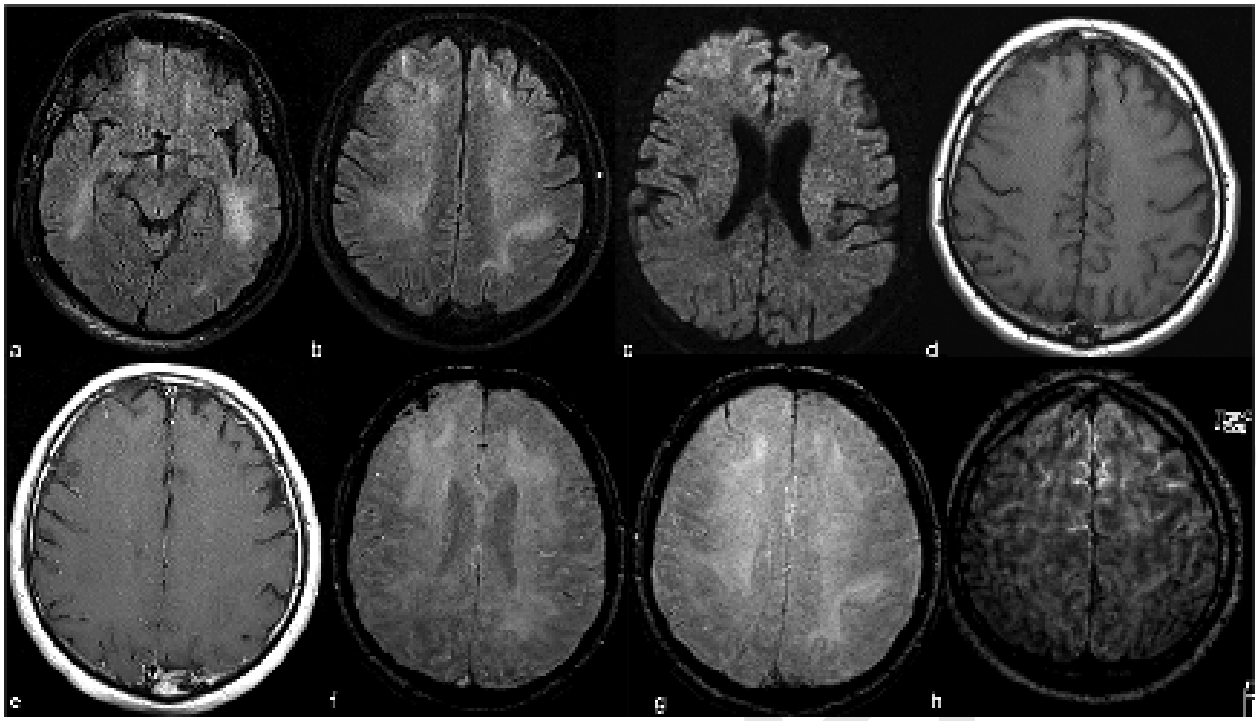

Figure 2. Contrast-enhanced cranial 1.5T MRI examination of a 59-year old intubated male patient with altered mental status despite tapering of sedoanalgesia. Axial FLAIR images at level of midbrain (a) and centrum semiovale (b) demonstrate prominent symmetric white matter hyperintensity and right frontal cortical hyperintensity. There is also prominent linear hyperintensity within frontal sulci. Axial b2000 DWI (c) shows frontal increased signal with corresponding low ADC (images not provided). Axial T1WI (d) shows right frontal sulcal effacement. Post-contrast T1WI (e) shows mild pial-subarachnoid enhancement. Axial SWI at the level of corona radiata (f) and centrum semiovale (g) demonstrates blooming artifact in the frontal sulci. Post-contrast FLAIR (h) depicts the bilateral leptomeningeal enhancement. ADC apparent diffusion coefficient; FLAIR fluid-attenuated inversion recovery; SWI susceptibility weighted image.

Appendix E1

Methods

Indications and timing for brain MRI in patients with mechanic ventilation was decided on a protocol established by ICU teams. Patients with ventilator support in ICU were managed in accordance with the guidance of Surviving sepsis campaign (17). According to this protocol, level of sedoanalgesia was gradually decreased, as positive end-expiratory pressure (PEEP) is decreased. Sedation was stopped for PEEP levels below 6 cm H_20, and neurologic status of patients were checked 24 hours later for level of consciousness and response to stimuli. If patients decreased level of consciousness persisted after another 24 hours, cranial MRI would be performed for further assessment of underlying CNS related changes. This protocol was followed in majority of cases; however there was variation in MR scanner availability dedicated to COVID-19 patients across institutions which limited the number of MRI scans performed in some of the institutions. Indications for patients with noninvasive ventilator support in ICU were decided on a case-by-case basis based on pathologic neurologic signs.

MR sequences included post-contrast and susceptibility series in addition to conventional sequences. Majority of the cases had the following sequences: Axial TSE T1, TSE T2, FLAIR, SWI, 3D TOF, sagittal TSE T2, coronal fat-saturated TSE T2, post-contrast axial TSE T1, post-contrast sagittal 3D TurboFLASH T1 with multiplanar reconstructions, post-contrast sagittal 3D Flair (3D SPACE) with multiplanar reconstructions. However in three cases post-contrast series could not be obtained due to patient's intolerance and in two cases only limited exam (DWI and FLAIR alone) could be acquired. COVID-19 related cranial MRI findings were evaluated by consensus of reviewers for dominant pattern of involvement including leptomeningeal, cortical, subcortical white matter, deep white matter, corpus callosum, deep gray matter, brain stem and cerebellar structures. For cases with cortical signal abnormalities, particular attention was paid to presence of subtle hemorrhagic changes or leptomeningeal enhancement. Additionally, acute ancillary findings such as acute cerebrovascular disease, venous thrombosis, and chronic parenchymal changes were also reviewed.

Although CT was used in ICU patients to exclude hemorrhage and large vessel occlusion, CT studies were not included due to low sensitivity for subtle parenchymal and/or meningeal abnormalities.

Results

Full description of MRI findings:

Twelve of 27 (44%) patients with MRI were abnormal. COVID-19 related neuroimaging findings were identified in 10/27 (37%) cases as cortical FLAIR signal abnormality (Fig 2; Appendix Figs E1-E4). Among these 10 cases; increased cortical diffusion weighted signal with corresponding low ADC values was seen in 7 cases, subtle leptomeningeal enhancement in 5 cases (out of a total of 8 cases that received contrast), and punctate cortical blooming artifact in 3 cases. In one case, leptomeningeal enhancement was seen only on post-contrast 3D FLAIR images and was not discerned on post-contrast T1WI or TurboFlash T1WI images (Appendix Fig E4). Accompanying subcortical and deep white matter signal abnormality on FLAIR images was seen in 3 and 3 cases, respectively. No case of corpus callosum, deep gray matter or infratentorial involvement was identified. The distribution of cortical signal abnormality was not specific and involved the frontal lobe in 4 cases, parietal in 3, occipital in 4, temporal in 1, insular cortex in 3 and cingulate gyrus in 3 cases. CSF was obtained in 5 out of 10 cases with cortical signal abnormality identified on MRI. Total protein was elevated (mean 79.9 mg/dL, range 59.9 – 109.7 mg/dL) in 4 of these patients. The cell count, glucose levels, IgG index, albumin were within normal limits, and RT-PCR for HSV DNA and SARS-CoV-2 were negative in all 5 specimens. Oligoclonal bands were checked in 3 specimens and were negative. Acute intracranial findings in the absence of cortical FLAIR signal abnormality included a case of acute transverse sinus thrombosis with no additional findings and a case of acute infarction in right MCA territory.

In 15/27 cases (55.6%), MR did not reveal any COVID-19 related or acute intracranial findings. CSF was obtained in two of these cases which showed elevated CSF protein despite negative MRI.

Chronic parenchymal changes or non-COVID-19 related findings included chronic small vessel

ischemic changes in 4 cases, infarct sequel in 4 cases, parenchymal atrophic changes in 3 cases, cavernoma in 1 case and intracranial metastatic lesion in 3 cases.

Anosmia was not a dominant symptom in this patient group and was detected in a single case (Appendix Fig E2).

Appendix figures:

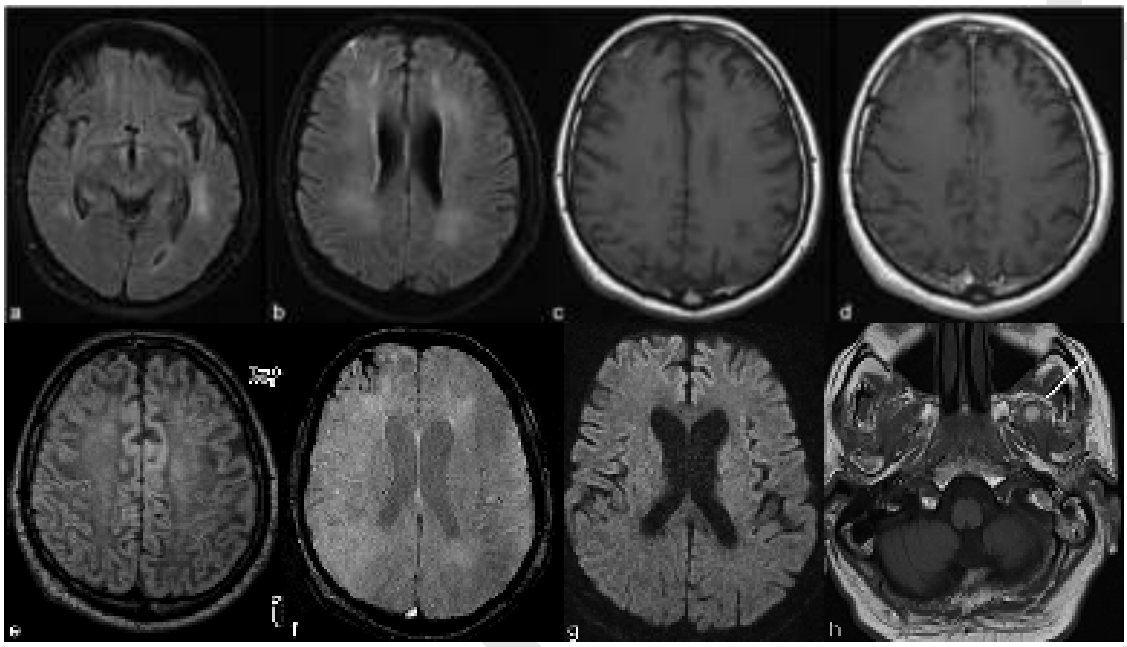

Figure E1. Control MRI of the 1st patient after 6 days. Axial FLAIR images at level of midbrain (a) and centrum semiovale (b) show interval regression of the white matter hyperintensities. Axial T1WI (c) shows persistence of sulcal effacement and a new focus of right frontal subacute hemorrhage. On post-contrast T1WI (d), there is still mild cortical enhancement, but post-contrast FLAIR (e) image shows complete resolution of pial-subarachnoid enhancements. Axial SWI (f) clearly depicts interval progression of blooming in the right frontal lobe. Axial DWI (g) demonstrates only mild parafalcine frontal cortical diffusion restrictions. As an ancillary new finding in the follow-up MRI, a round hyperintense mass compatible with subacute hemorrhage is seen in the left lateral pterygoid muscle (arrow) on axial T1WI (h) at the level of skull base.

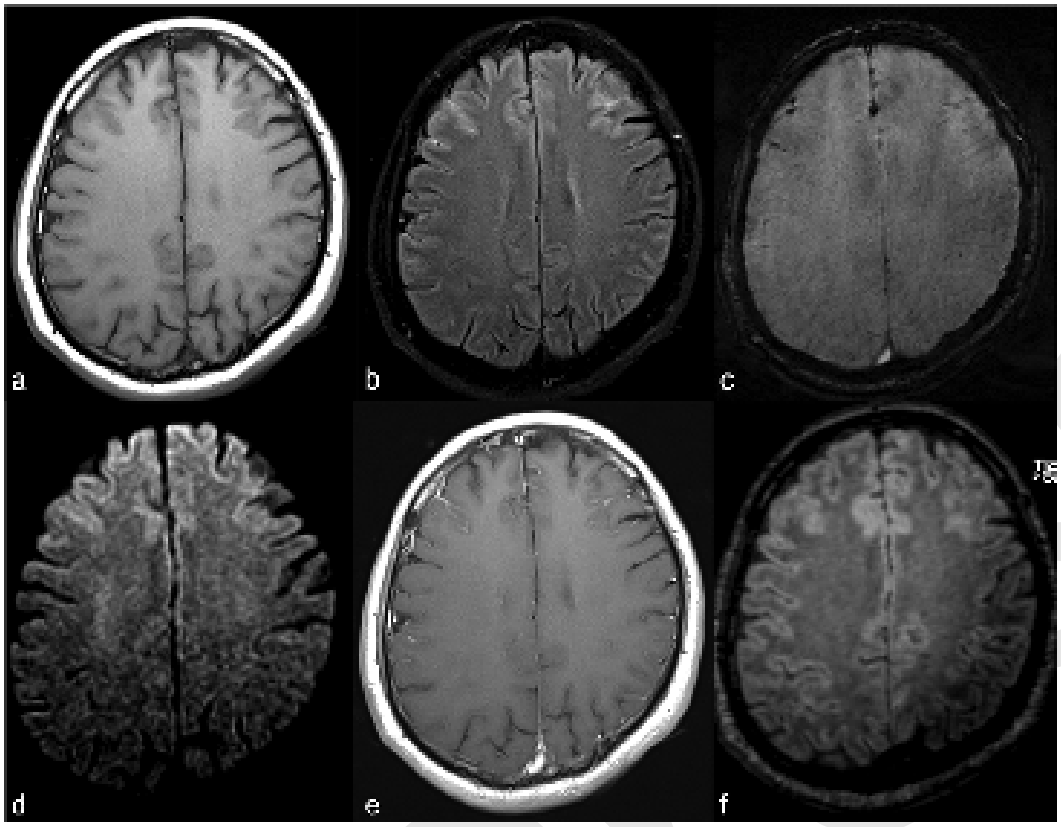

Figure E2. Contrast-enhanced cranial MRI of a 48 year-old intubated male patient with COVID-19 infection. Patient had anosmia in addition to the respiratory distress during his initial admission to ICU. MRI was performed due to decreased level of consciousness despite tapering of analgesia and improvement of respiratory status. Axial precontrast T1WI (a) demonstrates only subtle bifrontal sulci effacement. Axial FLAIR (b) without contrast shows bifrontal cortical hyperintensity. There is also pial-subarachnoid prominent linear hyperintensity scattered in some of the right frontal sulci, seen as blooming artifact on SWI (c). b2000 DWI (d) shows bilateral frontal cortical increased signal with corresponding low ADC (not shown). Post-contrast axial T1WI (e) demonstrates corresponding bilateral frontal mild linear enhancement. Post-contrast axial FLAIR (f) image only shows cortical hyperintensity without pial-subarachnoid enhancement.

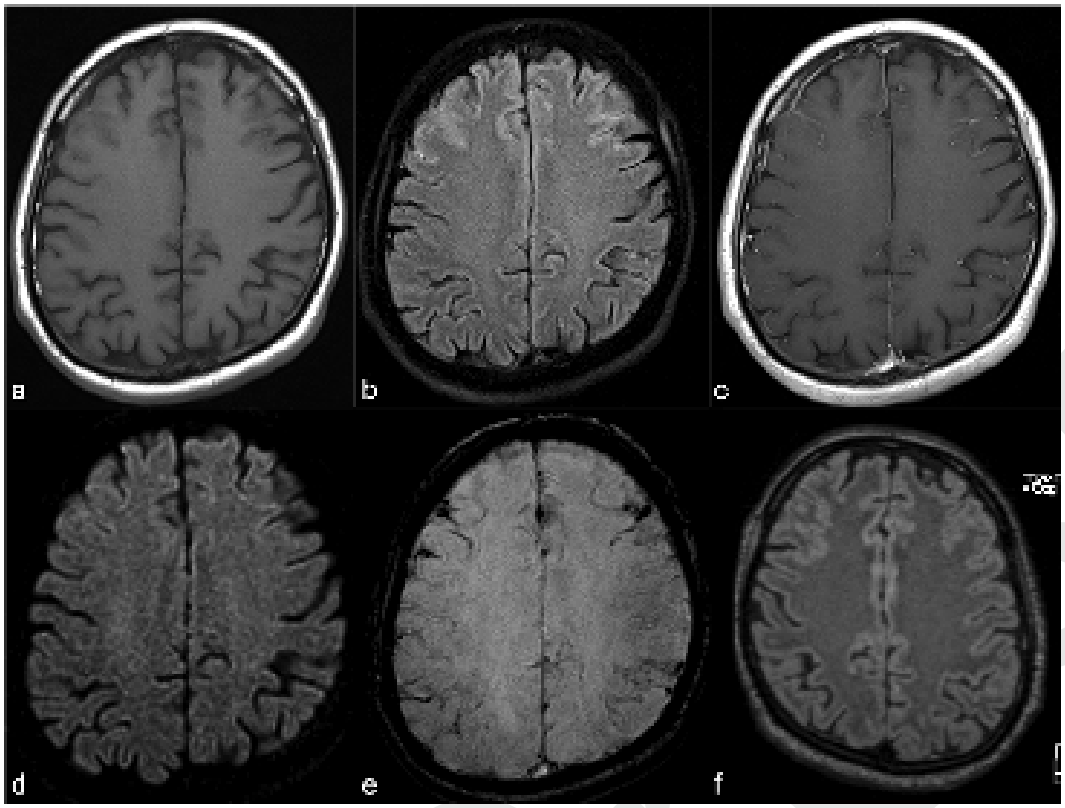

Figure E3. Control MRI of the 2nd patient after 7 days. Axial T1WI (a) without contrast demonstrates only mild bifrontal sulci effacement. Axial FLAIR (b) shows persistence of similar findings compared to the prior imaging. There is also stable mild cortical enhancement on post-contrast axial T1-WI (c). There is total regression of DWI (d) findings. On the contrary, SWI (e) demonstrates interval progression of the blooming artifacts. On post-contrast FLAIR (f) image, there is only mild cortical hyperintensity without enhancement.

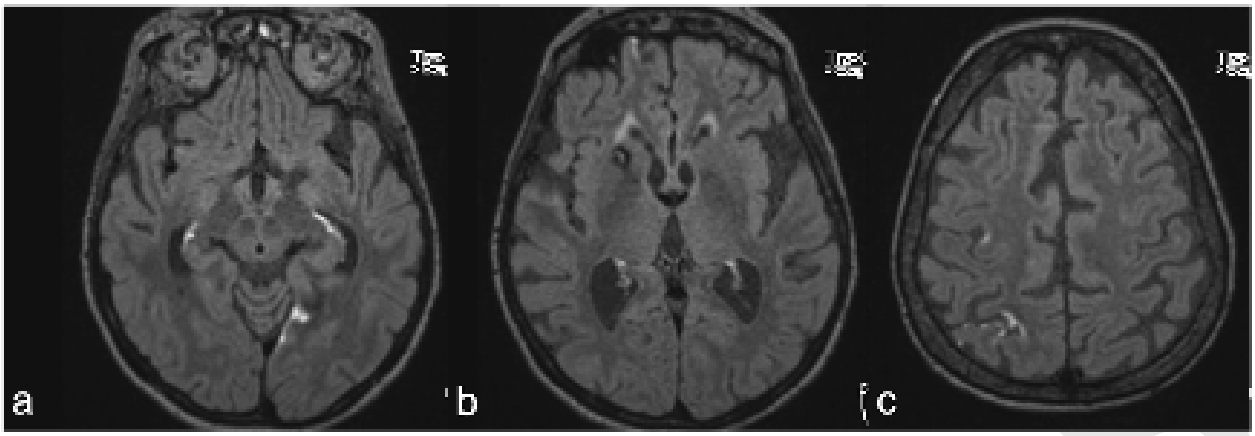

Figure E6. 69 year-old intubated female patient. Post-contrast 3D FLAIR images (a-c) show mild linear pial-subarachnoid enhancement in the left occipital lobe (a), right parietal (b) and posterior frontal lobes (b). There is an incidentally noted cavernoma adjacent to the head of right caudate nucleus (c). These enhancements are only depicted on post-contrast 3D FLAIR images with no discrete evidence of enhancement on the post-contrast T1WI and post-contrast TurboFlash T1WI (images not provided). Increased protein level was depicted in CSF analysis.

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