Neuroimaging Spectrum in COVID-19 Infection: A Single-Center Experience

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Abstract

Background and Purpose The ongoing coronavirus disease 2019 (COVID-19) pandemic is a multisystemic disease and involvement of the nervous system is well established. The neurological and neuroimaging features of the disease have been extensively evaluated. Our study aimed to elucidate the neuroradiological findings in COVID-19 infected patients admitted to our institute during the first and second waves of the pandemic in India.

Methods This was a single-center retrospective study of all COVID-19 positive patients who underwent neuroimaging between March 2020 and May 2021. The presenting neurological complaints, the imaging findings in computed tomography (CT) imaging, and/or magnetic resonance imaging (MRI) were recorded. They recorded the findings in the subheadings of ischemic stroke, hemorrhagic stroke, parainfectious demyelination, acute encephalitis syndrome, and changes of global hypoxic changes. Patients with age-related, chronic, and incidental findings were excluded.

Results The study comprised of 180 COVID-19 positive patients who underwent neuroimaging. CT scan was performed for 169 patients, MRI for 28, and a combination of both CT and MRI was performed for 17 patients. Seventy percent of patients were males, and median age was 61.5 years (interquartile range: 48.25–70.75). Out of the 180 patients, 66 patients had nonspecific findings that could not be attributed to COVID-19 infection. In the remaining 114 patients, 77 (42.7%) had ischemic findings, while 22 (12.2%) had hemorrhagic stroke. Hypoxic ischemic changes were noted in five patients. The rest of the patients had a spectrum of changes including, cerebellitis (3), tumefactive demyelination (1), COVID-19-associated encephalitis (1), hemorrhagic

Keywords
- cerebellitis
- COVID-19
- COVID-19-associated encephalitis
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acute demyelinating encephalomyelitis (1), transverse myelitis (1), cytotoxic lesions of corpus callosum (1), Guillain-Barre syndrome (1), and COVID-19-associated microhemorrhages (1).

Conclusion Neurological manifestations of COVID-19 infection are not uncommon, and our understanding of this topic is expanding. A complex interplay of neurotropism and direct central nervous system invasion, immune activation and cytokine storm, vasculitis, and parainfectious processes are implicated in the pathophysiology. While the most common imaging finding was ischemic stroke, followed by hemorrhagic stroke, a diverse range of parainfectious findings was also noted in our study.

Introduction

The World Health Organization classified coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus, as a pandemic on March 11, 2020.[1] What started as a respiratory infection was later discovered to be a multisystem disease with an affinity for the nervous system as well. As the pandemic evolved, it became clear that neurological symptoms were common and ranged from mild symptoms like anosmia, dysgeusia, and headache to severe central nervous system symptoms like seizures, focal neurological deficit, and acute altered mental status.[2,3]

The current literature suggests that direct viral invasion and hyperimmune related reactions are the two main pathophysiological factors associated with neurological manifestation. The direct viral invasion of the neurons and cerebral vessel endothelium through the hematological, transcribrial, and neuronal retrograde dissemination pathways is thought to be responsible for anosmia, encephalitis, and vasculitis, whereas the immune hyperactivation and cytokine storm are responsible for the hypercoagulable state responsible for thromboembolic and hemorrhagic syndromes.[4,5] Further, a delayed immune response is also linked to Guillain-Barre syndrome and acute demyelinating encephalomyelitis (ADEM) like manifestation.[5,6]

This study analyzes the spectrum of neuroimaging findings during the first and second waves of COVID-19 infection admitted at out facility.

Materials and Methods

After approval from the institutional ethics committee, a retrospective review of neurological imaging of patients with the reverse transcription-polymerase chain reaction (RT-PCR positive) and/or COVID-19 Reporting and Data System category-5 on high-resolution computed tomography of thorax was performed. The study comprised of patients from both the first and second waves of COVID-19 pandemic who were scanned between March 2020 and May 2021. Available computed tomography (CT) and/or magnetic resonance imaging (MRI) data were systematically recorded and analyzed. COVID-19 suspect cases who turned out to be RT-PCR negative and whose chest findings did not corroborate with a diagnosis of COVID-19 were excluded from the study.

Clinical and Imaging Data

Clinical and demographic data, including age and sex, coexisting comorbidities, mean duration of onset of symptoms, clinical presentation, inflammatory markers, and outcome, were collected. CT head was performed on Siemens SOMATOM Definition Flash Dual Source Dual Energy 128×2 slices CT scanner and Siemens SOMATOM Definition Drive Dual Source Dual Energy 128×2 slice CT scanner. In addition, CT angiography was performed in patients who had an acute focal neurological deficit or a nonhypertensive pattern of hemorrhage on plain CT head. MRI was performed on a 3T scanner (GE Discovery MR750w) and included axial T1-weighted imaging (T1WI), axial T2WI, three-dimensional fluid-attenuated inversion recovery, diffusion, and susceptibility-weighted images. Whenever indicated, post-contrast T1WIs, MR Angiogram, and MR venogram were obtained.

The MRI and CT studies were evaluated by two experienced radiologists in consensus (PG & ST with experience of 11 and 8 years, respectively). The imaging features were recorded in the subheadings of ischemic stroke, hemorrhagic stroke, parainfectious demyelination, acute encephalitis syndrome, and changes of global hypoxic changes. Patients with age-related changes and incidental findings, which were not related to ongoing COVID-19 infection were excluded with consensus.

Large vessel occlusion was defined as occlusion of the internal carotid artery, the M1 and M2 segments of middle cerebral artery, the P1 and P2 segment of posterior cerebral artery, the basilar trunk, the intracranial vertebral artery, and the posterior cerebral artery.[7] The small vessel occlusion included infarcts secondary to occlusion of perforating vessels, deep penetrating branches of cerebral vessels from the circle of willis.[8]

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Corp, Armonk, IBM Corp, United States). Qualitative variables like age, gender, comorbidities, clinical symptoms, and imaging features were described by frequency and percentages.

Result

A total of (5821) COVID-19-positive patients were admitted between May 2020 and May 2021 out of which 180 patients underwent imaging for neurological symptoms. CT scan was performed for 169 patients, MRI for 28 and a combination of both CT and MRI was performed for 17 patients. CT brain was the most used investigation modality, and MRI was reserved for cases where the clinical condition was not explained by the CT images. The median age was 61.5 years (interquartile range: 48.25–70.75). Male patients comprised 70% (126) and females 30% (54) of the study cohort. The most frequent complaint was of a focal neurological deficit (40%), presenting with weakness of either side of the body with or without aphasia and cranial nerve deficits. The next most common presentation was with altered sensorium (37.8%) followed by headache (16.2%). Other complaints were generalized weakness (3.8%), seizures (2.7%), giddiness, and vertigo (3.9%).

Of these 180 patients, who underwent neuroimaging with either CT and/or MRI brain 66 (36.6%) patients had findings not related to COVID-19 infection (►**Fig. 1**). Most of these were recorded as normal study, age-related atrophic changes, or changes not related to the co-existing COVID-19 infection. Among the 114 patients with acute or subacute findings on CT/MRI of neuroaxis, features of acute or subacute ischemic stroke were the most common and were recorded in 77 patients (42.7%; 77 out of 180). On further subclassification, 52 of these 77 patients (67.5%) had large vessel occlusions, 19 (24.6%) had small vessel occlusions, and 6 (7.8%) patients had watershed infarcts. A unique feature reported in 11 patients (14.2%) was the presence of a free-floating thrombus (FFT) in the major neck arteries, predominantly involving the common carotid bifurcation. Of these 11 patients, 10 had major vessel occlusion and only one patient had small vessel occlusion.

Hemorrhagic stroke was reported in 22 patients (12.2%), with 11 cases of parenchymal hemorrhage, 6 cases of aneurysmal hemorrhage, 2 patients with nonaneurysmal subarachnoid hemorrhage, 2 cases of cerebral venous sinus thrombosis, and 1 case of subdural hemorrhage. Of the parenchymal hemorrhages, two cases were secondary to anticoagulation use. The majority of intraparenchymal hemorrhages occurred in the gangliocapsular (5 cases) and thalamic regions (3 cases).

Other imaging findings associated with COVID-19 infection in this study cohort included cerebellitis (3 patients), tumefactive demyelination (1 patient), COVID-19-associated encephalitis (1 patient), hemorrhagic ADEM (1 patient), COVID-19-associated transverse myelitis (1 patient), COVID-19-associated cytotoxic lesion of the corpus callosum (1 patient), Guillain-Barre syndrome (1 patient), and COVID-19-associated microhemorrhages (1 patient). These patients represent changes secondary to direct viral invasion, parainfectious, or postinfectious conditions. Further, hypoxic ischemic changes were reported in 5 patients on imaging.

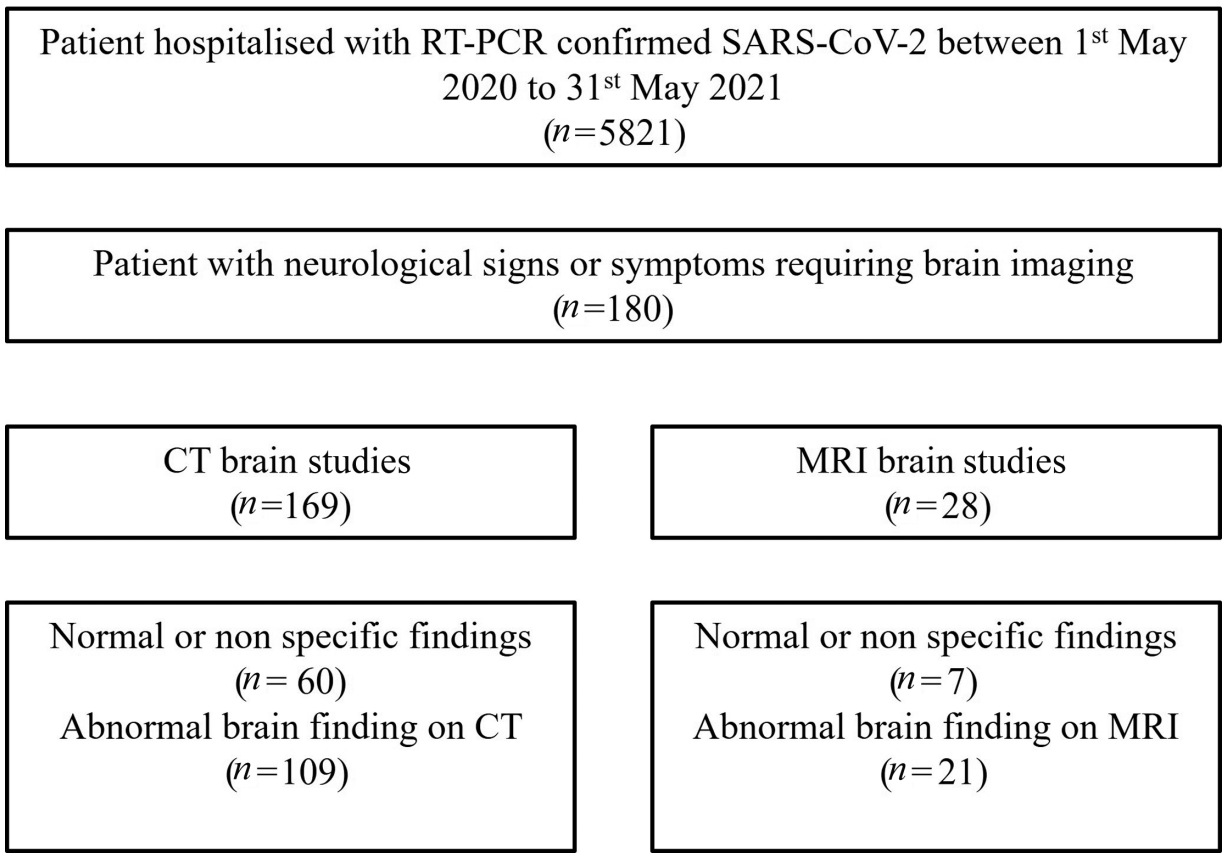

Fig. 1 Flowchart showing patient imaged for coronavirus disease 2019 infection. CT, computed tomography; MRI, magnetic resonance imaging; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Discussion

The COVID-19 infection is caused by a single-stranded, positive-sensed RNA virus (SARS-CoV-2) with multisystem involvement. Although mild-to-moderate pulmonary manifestations are the most frequent presentation, about one-third of patients have neurological manifestations[9,10] and 14 to 17% of admitted patients will require neuroimaging.[11,12] The involvement of both the central and peripheral nervous system is well established in patients with COVID-19 infection, and this apparent neurotropism could be attributed to the widespread expression of angiotensin receptor enzyme-2 in the endothelial cells, glial cells, and astrocytes in the nervous system.[13] This expression is enhanced in coexisting comorbidities like diabetes and hypertension.[14] Other implicated mechanisms of neuro invasion are invasion of olfactory epithelium, the Trojan horse mechanism of leucocyte invasion, and subsequently bypassing the blood–brain barrier and trans-synaptic spread via the nerve terminals of the vagus nerve.[5]

In addition to direct central nervous system (CNS) invasion, other mechanisms of neurological involvement include parainfectious effects with immune hyperactivation and cytokine storm, delayed postinfectious immune response, complications arising from prolonged hospitalization, and drug-related effects.[15]

Ischemic stroke was the most common neuroimaging feature in our cohort of admitted patients with COVID-19, accounting for 42.7% of cases, of which more than two-thirds were large-vessel occlusion with territorial infarction and the rest were secondary to small vessel occlusion or watershed infarcts. Thus, a larger proportion of patients had large vessel occlusion. This contrasts with noninfected population where the incidence of large vessel usually ranges between 24 and 35% stroke (►**Fig. 2**).[16,17] In addition, 14% of the patients had FFT in major arteries, which accounted for one-fifth of the overall large vessel occlusion stroke load. This is a considerable rise from the average incidence of FFT in stroke patients, which is 1.53% (►**Fig. 3**). A proinflammatory environment with cytokine storm, endothelial dysfunction, and activation of the coagulation cascade promoting a hypercoagulable state is responsible for the increased incidence of stroke in COVID-19 infection.[18–20]

Hemorrhagic stroke was reported in 22 patients in our cohort (12.2%) of cases. Half of these were parenchymal hemorrhage, of which two cases were secondary to anticoagulation use. Subarachnoid hemorrhage was reported in eight cases, of which six were aneurysmal rupture and two

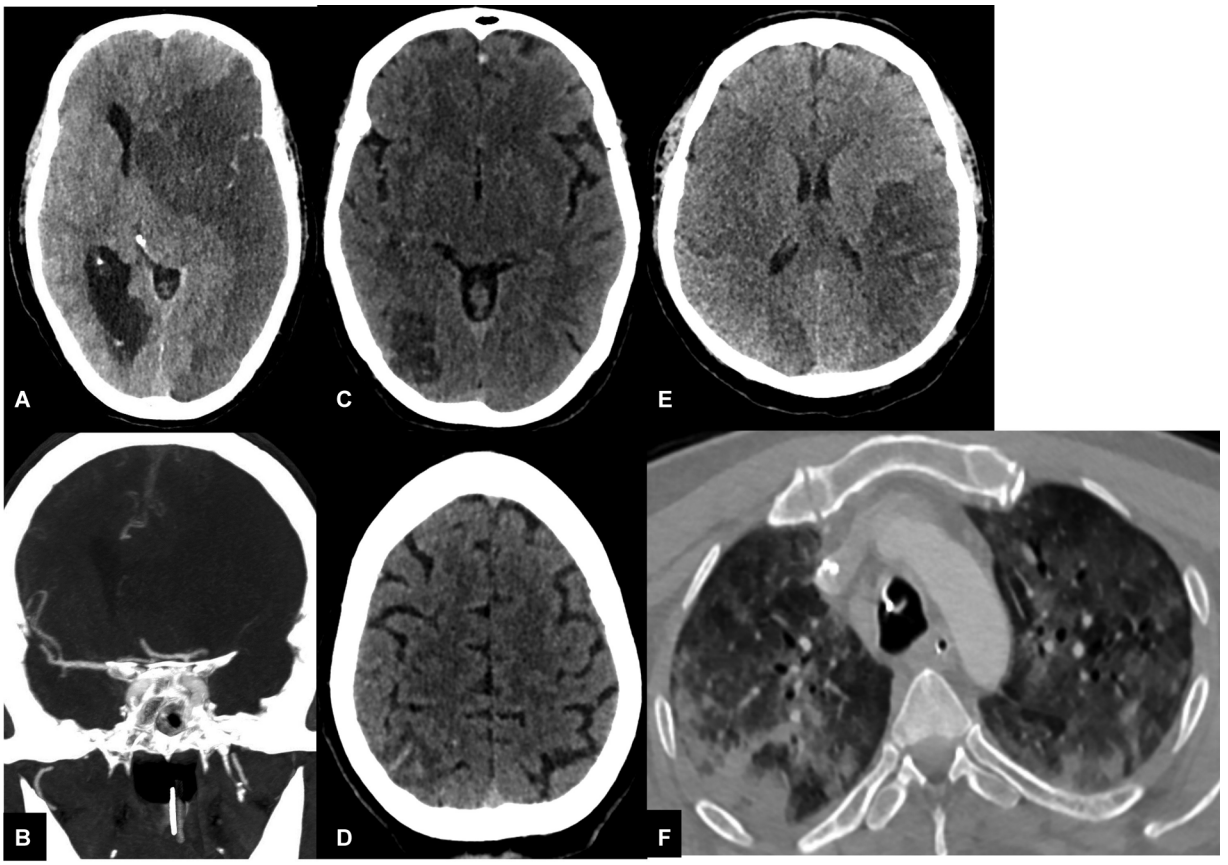

Fig. 2 Acute ischemic stroke in coronavirus disease 2019 (COVID-19) patients. A 71-year-old COVID-19-positive patient presenting with right-sided hemiplegia of 48 hours duration. The axial noncontrast computed tomographic (CT) images (**A**) show complete left middle cerebral artery (MCA) territory infarct with significant mass effect and midline shift, with occlusion of the proximal M1 segment of left MCA on coronal CT angiogram maximum intensity projection image (**B**). Another patient with left hemiparesis shows embolic infarcts at right occipital and superior parietal lobule (**C** and **D**). Sudden decrease in Glasgow coma scale score in an intubated patient shows bilateral middle cerebral artery infarcts (**E**). Note the peripherally oriented opacities in bilateral upper lung fields (**F**).

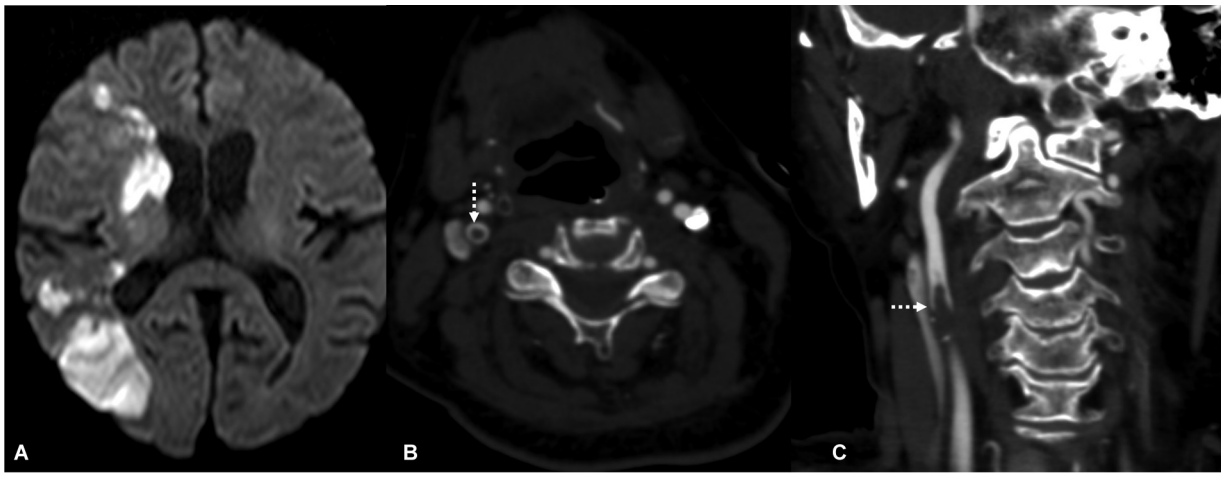

Fig. 3 Free-floating thrombus in coronavirus disease 2019 (COVID-19) infection: A 55-year-old male, COVID-19 positive on 10th day of his illness, developed sudden weakness of left side of the body. The axial diffusion-weighted image (**A**) shows patchy diffusion restricting acute infarct in right middle cerebral artery territory and watershed zone. The axial (**B**) and coronal (**C**) images of computed tomographic angiogram of neck vessel reveal a free-floating thrombus with plaque at right carotid bulb extending into the proximal internal carotid artery (dashed white arrows). These free-floating thrombi are frequent association with COVID-19 infection.

were nonaneurysmal subarachnoid hemorrhage (►**Fig. 4**). The increased turnover and instability of arterial collagen are postulated to be related to an increased risk of aneurysmal rupture and subarachnoid hemorrhage. This mechanism is mediated by modulation of matrix metalloproteinase 2 enzyme expressed on the arterial basement membrane by the virus. Another mechanism is the vascular injury induced by the cytokine storm and elevated levels of interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha.[21,22] On the other hand, nonaneurysmal subarachnoid hemorrhage is linked to

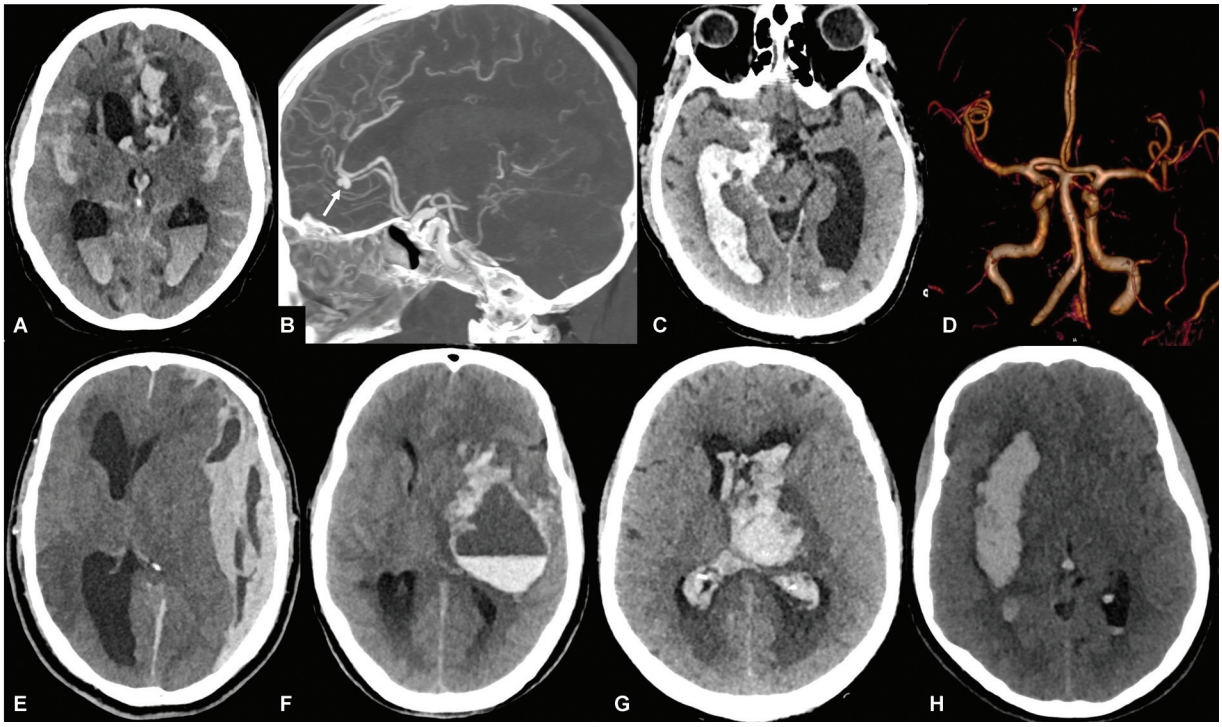

Fig. 4 The hemorrhagic manifestations of coronavirus disease 2019 (COVID-19) infection. A 76-year-old female with severe headache and altered sensorium (**A** and **B**) showed diffuse subarachnoid hemorrhage and left distal anterior communicating artery aneurysm (arrow). A 65-year-old male, COVID-19 positive, presents with severe headache. Imaging revealed (**C** and **D**) subarachnoid hemorrhage at right side of suprasellar cistern and crural cistern with intraventricular extension. The volume rendered images of magnetic resonance angiogram do not reveal any aneurysm, consistent with angionegative subarachnoid hemorrhage. Image (**E**) shows a large left frontoparietal subdural hemorrhage with fluid levels in a 75-year-old patient with COVID-19 infection. The axial computed tomographic image (**F**) shows a large left gangliocapsular hematoma with hematocrit effect in a 40 years old male patient, who was on anticoagulation because of raised D-dimer levels. The image (**G**) and (**H**) show two young patients (28 and 17 years, respectively) presenting with intraparenchymal hemorrhage during their ongoing COVID-19 infection.

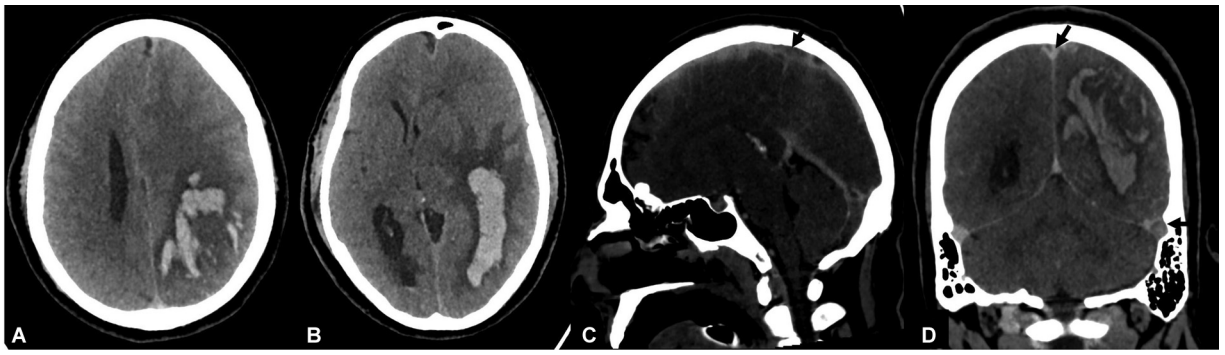

Fig. 5 Cerebral venous sinus thrombosis with coronavirus disease 2019 (COVID-19) infection: 48 years/male presented with headache with fluctuating dysarthria on day 12 of COVID-19 infection. The noncontrast computed tomography (CT) scan (**A** and **B**) shows intraparenchymal hemorrhage at left parietotemporal region with moderate perilesional edema and mass effect. The contrast-enhanced CT (**C** and **D**) shows thrombus within the mid-third of superior sagittal sinus and the left transverse–sigmoid sinus (black arrow).

microthrombosis with secondary hemorrhage, coagulation dysfunction such as disseminated intravascular coagulation, and cytokine storm induced endothelitis.[23,24] Though the causal relation of subarachnoid and intraparenchymal hemorrhage with COVID-19 infection is not established, we did find increased severity and mortality in our patient cohort. Cerebral venous sinus thrombosis was reported in only two patients (1.11%) in our cohort; thus, it was a rare association with COVID-19 infection (►**Fig. 5**).

The study cohort includes three patients presenting with cerebellitis (2 pediatric cases and 1 adult), manifested with obstructive hydrocephalus, and altered sensorium during active COVID-19 infection and needed ventricular drainage (►**Fig. 6**). There are isolated case reports of COVID-19-associated cerebellitis in both adult and pediatric populations and it is proposed to be secondary to direct viral neurotropism or immune mediated injury.[25,26] We report one case of encephalitis associated with COVID-19, who presented with seizure, encephalopathy, and left hemiparesis (►**Fig. 7**). COVID-19-associated meningitis and encephalitis are uncommon with an incidence of 0.03 to 0.1%.[27] We also report COVID-19-associated acute transverse myelitis and paraspinal myosotis. It is rare and represents parainfectious and postinfectious process.[28] Paraspinal myositis is proposed to be secondary to direct muscular viral infection with SARS-CoV-2 or parainfectious inflammatory process (►**Fig. 8**).[29]

We report one case each of tumefactive demyelination and hemorrhagic acute demyelinating encephalomyelitis (►**Figs. 9** and **10**). Both patients presented with acute onset encephalopathy in the background of ongoing COVID-19 infection. Only one case of tumefactive demyelination associated with COVID-19 infection has been published in the literature.[30] An increased incidence of ADEM has been reported in COVID-19 pandemic. A systematic review of COVID-19-associated ADEM revealed a longer duration between the onset of the antecedent infective symptoms and the start of ADEM symptoms, the older age distribution of the patients, relatively poor outcome, and more predilection of periventricular white matter and splenium of the corpus callosum on imaging.[31]

COVID-19-associated cytotoxic lesions of the corpus callosum was reported in one patient. MRI revealed diffusion restriction in the splenium and posterior part of the body of corpus callosum, in bilateral corona radiata, and posterior limb of internal capsules (►**Fig. 11**). Although it is typically described in children, our patient was an adult. Hyperinflammatory response and cytokine storm with selective vulnerability of the corpus callosum splenium to cytokinopathy are thought to be the cause.[32,33]

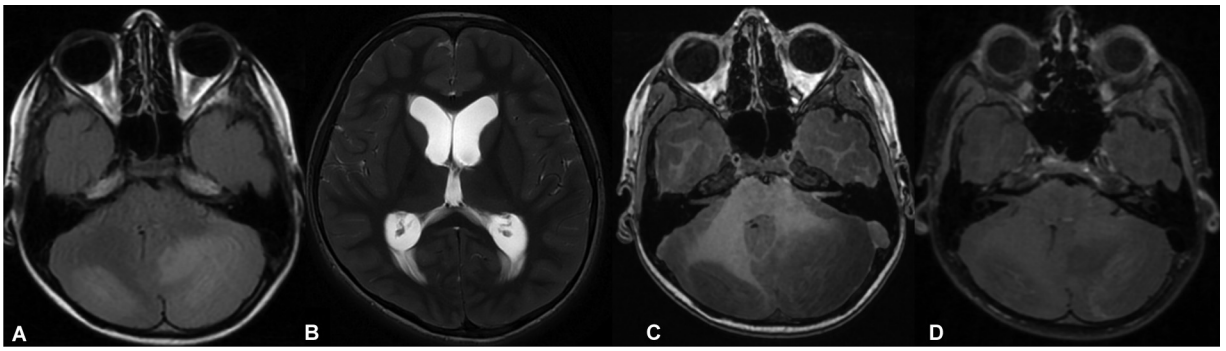

Fig. 6 A 12-year-old boy presented with fever 7 days with headache and altered sensorium, diagnosed coronavirus disease 2019 (COVID-19) on presentation. The axial MRI (**A**, **B,** and **C**) images show asymmetrical FLAIR hyperintensity in bilateral cerebellum (left > right) with effacement of 4th ventricle leading to hydrocephalus. The postcontrast scan (**D**) shows ill-defined enhancement of cerebellar folias. The features are consistent with COVID-19 associated acute cerebellitis.

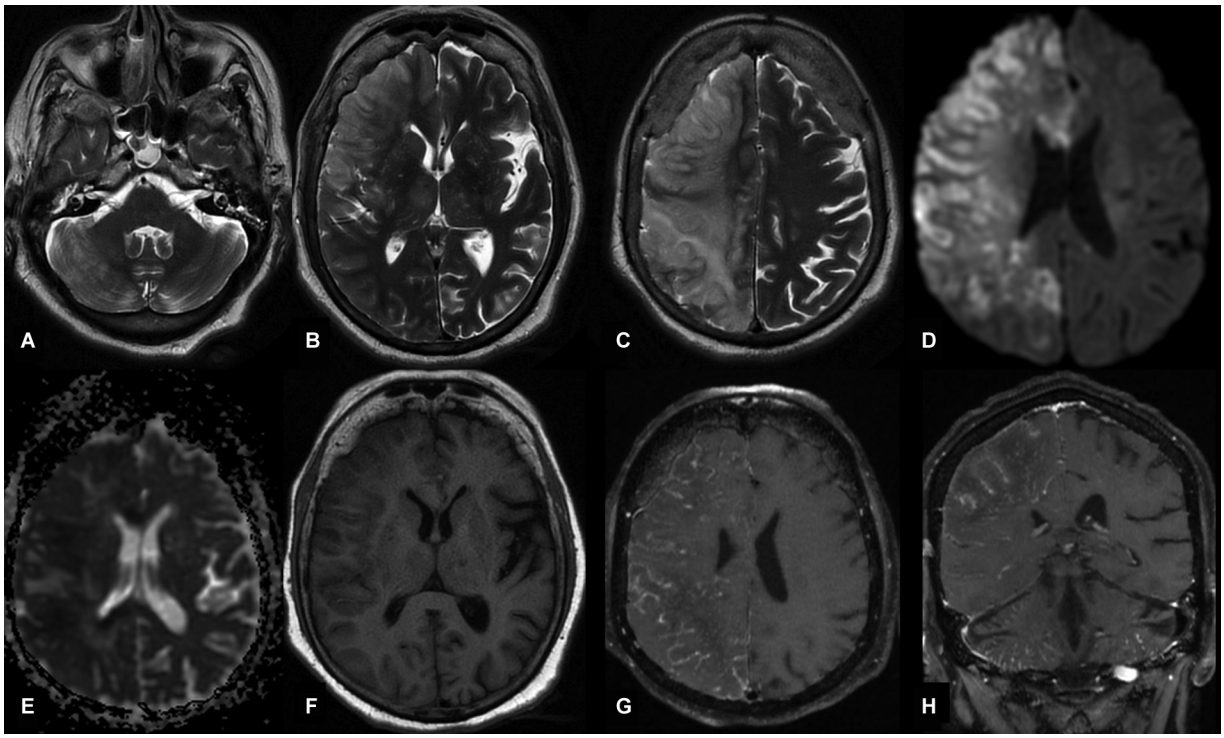

Fig. 7 A 84-year-old female with multiple comorbidities, admitted with coronavirus disease 2019 (COVID-19) pneumonia for 14 days, developed sudden left-sided hemiparesis with rapid deterioration of sensorium. The axial T2 images (**A**–**C**) show abnormal T2 hyperintensities involving the right cerebral hemisphere (cortical as well as white matter involvement) and the right cerebellum. Note the involvement of bilateral thalami. The diffusion image (**D**) and corresponding apparent diffusion coefficient image (**E**) show extensive diffusion restriction in the involved region. The precontrast axial (**F**), postcontrast axial (**G**) and coronal image (**H**) show leptomeningeal and ill-defined subcortical enhancement along bilateral cerebral and cerebellar hemisphere (right > left). Correlating with the clinical detail, the imaging features are consistent with COVID-19-related encephalitis.

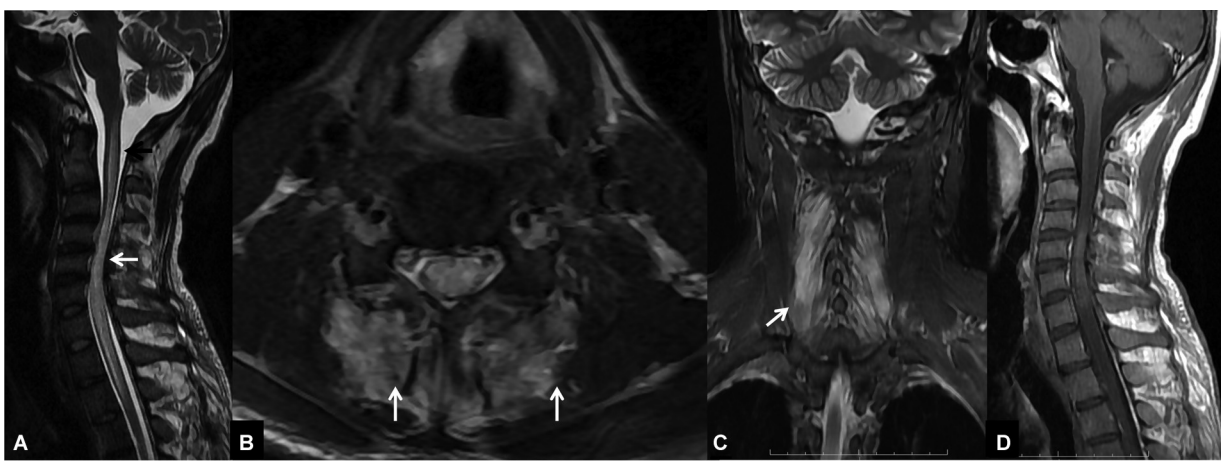

Fig. 8 A 30-year-old male with coronavirus disease 2019 (COVID-19)-positive status, presented with sudden onset quadriparesis for 2 days duration. The sagittal T2 image (**A**) shows long segment myelitis extending from cervicomedullary junction to D2 vertebra (white arrow). The axial T2 image (**B**) shows circumferential involvement of entire cord. Note the hyperintensity in the paraspinal muscle (white arrows) in axial T2 image (**B**) and coronal short tau inversion recovery (STIR) image (**C**). The postcontrast T1 image (**D**) shows faint enhancement of the cervical cord. These features are consistent with COVID-19 associated acute transverse myelitis with paraspinal myositis.

Cerebral microhemorrhages are a well-documented entity in critically ill patients with COVID-19 infection.[34] These microbleeds are predominantly subcortical and callosal in distribution. They are proposed to be secondary to severe hypoxia (akin to high altitude cerebral edema/ acute respiratory distress syndrome), consumption of coagulopathy, or COVID-19 induced endotheliitis. We could demonstrate this finding in only one patient, mostly because MRI data was available in limited cases (►**Fig. 12**). Our cohort also included a case of COVID-19-associated Guillain-Barre syndrome, showing enhancement of the cauda equina nerve roots.

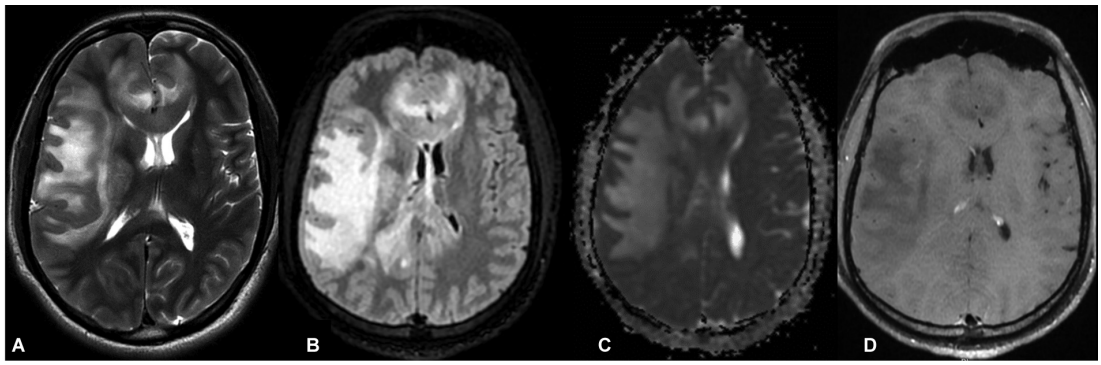

Fig. 9 A 35-year-old male presented with rapidly progressive sequential weakness of left upper limb followed by left lower limb, followed by focal seizure and altered sensorium. The axial T2 (**A**) and axial fluid-attenuated inversion recovery (**B**) show large tumefactive demyelinating lesion at right frontoinsular region, the corpus callosum, and the pericallosal white matter. The apparent diffusion coefficient image (**C**) of the diffusion weighted images does not show any restriction. The postcontrast T1 image (**D**) does not show any obvious contrast enhancement.

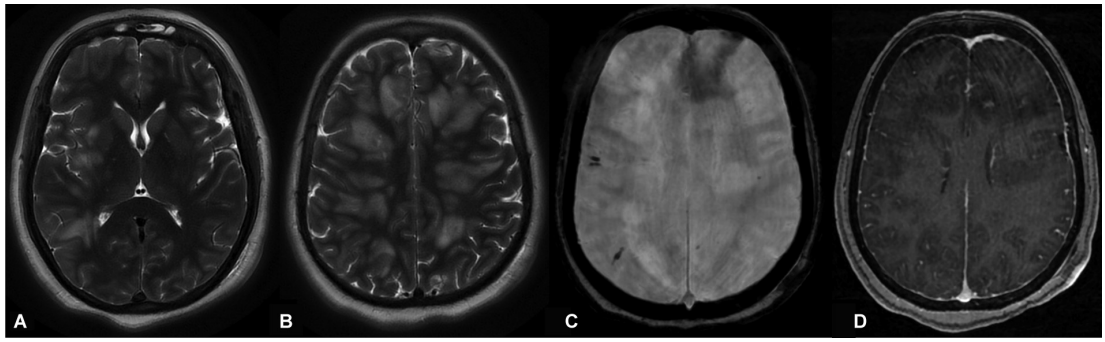

Fig. 10 A 50-year-old female with coronavirus disease 2019 positive status, history of fever for 7 days, presented with acute onset vomiting and altered sensorium. The axial T2 images (**A** and **B**) show fluffy hyperintense lesions in the subcortical white matter of bilateral cerebral hemisphere with involvement of right putamen. The susceptibility-weighted images show microhemorrhages in few of the lesions (C). The postcontrast scan (**D**) does not reveal any abnormal enhancement.

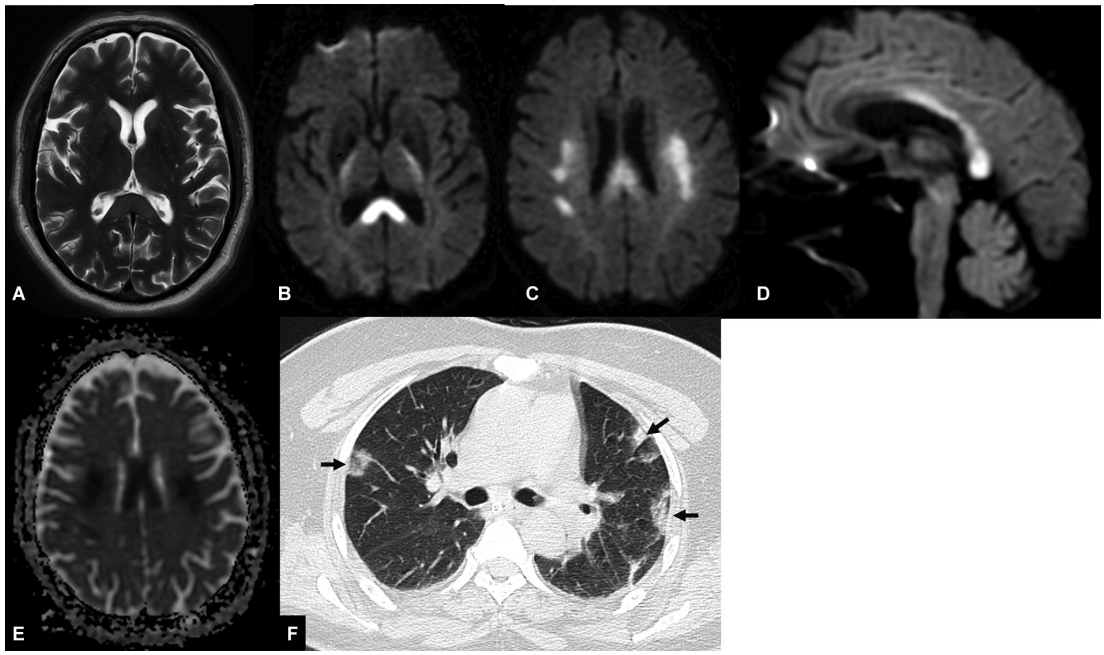

Fig. 11 A 65-year-old lady, coronavirus disease 2019 (COVID-19) positive, presented with altered sensorium. Evaluation ruled out any electrolyte disturbance. Magnetic resonance imaging revealed diffusion restriction in the splenium and posterior part of body of corpus callosum, in bilateral corona radiata and posterior limb of internal capsules (**A**–**E**). Note the classical peripherally oriented ground glass opacities in lung fields (black arrows) (**F**). These features are consistent with COVID-19-associated cytotoxic lesions of the corpus callosum.

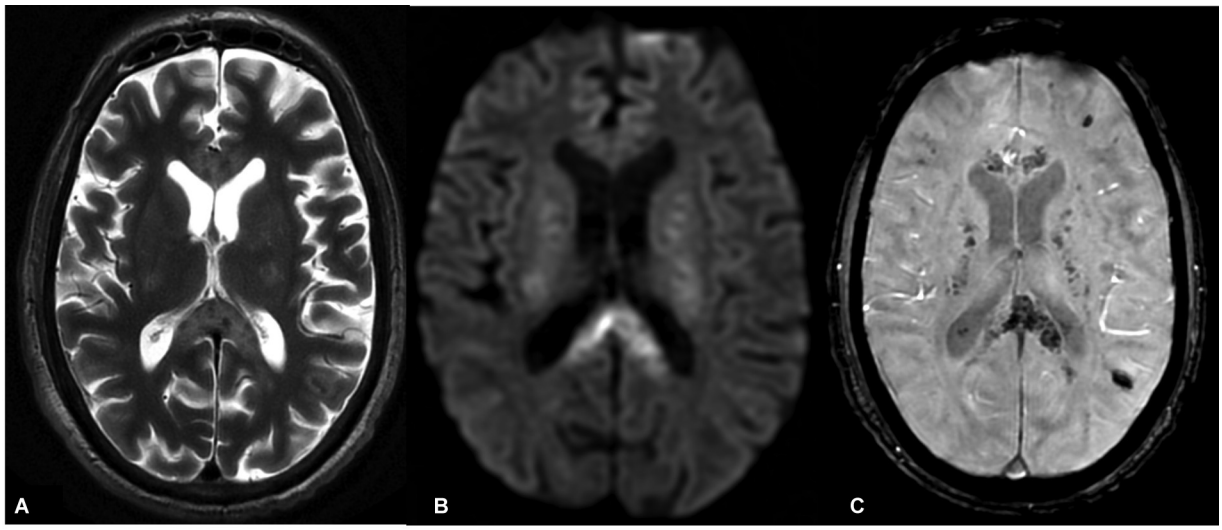

Fig. 12 A 65-year-old male, coronavirus disease 2019 (COVID-19) positive, with altered sensorium and need for mechanical ventilation. The axial T2 (**A**), diffusion-weighted image (**B**), and the susceptibility image (**C**) show multiple foci of micro- and macro-hemorrhages in corpus callosum, centrum semiovale, subcortical white matter, and internal capsule. These features are consistent with COVID-19-associated micro-hemorrhages.

Apart from the direct CNS invasion, hypoxia-related changes are also described in the CNS owing to respiratory involvement and impaired gas exchange at the alveoli-capillary level. Features of hypoxic ischemic insult were reported in five patients, with all of them having a fatal outcome.

The study has several limitations. First, CT scans were the most used imaging modality in most patients, with only a few cases undergoing MRI. This is particularly true for cases during the first wave and early part of the second wave. MRI was reserved for COVID-19 cases with clinical dilemma or with the highest clinical urgency. Second, the study includes the hospitalized patient with positive RT-PCR, hence postinfectious COVID-19-associated condition occurring during the convalescent phase could not be included. Third, this study had inherent limitations related to its retrospective nature.

Conclusion

As the COVID-19 epidemic has evolved, our understanding of the neurological presentation and neuroimaging findings linked with this illness has grown. We offer a view of neuroimaging characteristics for a tertiary care hospital in India, where ischemic and hemorrhagic stroke are the most common manifestations, as reported globally.

Conflict of Interest
None declared.

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