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REVIEW ARTICLE

Neurological Manifestations In COVID-19 Patients: An Imaging Review

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Abstract

Background: The COVID-19 pandemic that started in late 2019, has posed a great health challenge to India rapidly elevating our country to the second most affected nation after the United States. While the respiratory manifestations of COVID-19 are widely-known, there is paucity of information on its neurological manifestations in Indian literature. The imaging features of the diverse neurological presentations such as stroke, encephalitis, demyelination, hemorrhages and vascular involvement are reviewed in this article. Objective of the review is to discuss the spectrum of neuroimaging features in COVID-19. **Methods:** Multiple publications from systematic and cohort studies on neuroimaging are reviewed in this article. Due permission was obtained from the publishers to reproduce the illustrations because of lack of adequate neuroimaging data in our country. **Results:** Ischemic infarcts, micro-hemorrhages, parenchymal hematomas and white matter changes, both diffuse and focal were the most common manifestations. Acute necrotizing hemorrhagic encephalitis, features resembling posterior reversible encephalopathy syndrome (PRES) and acute demyelinating encephalomyelitis (ADEM), arterial dissections, dural sinus and deep venous thrombosis were reported. Olfactory bulb and white matter signal ratios were elevated in anosmic patients. Micro-structural changes such as remyelination and neurogenesis indicated processes of repair. **Conclusion:** Ischemic and hemorrhagic lesions are the most common neuroimaging abnormalities in COVID-19 patients, though 40% of the studies are normal. Awareness of the imaging features is essential for management of these patients in the current pandemic. Severity of illness and risk of spread of infection are major constraints for neuroimaging.

Key message: Neuroimaging features of COVID-19 patients have not received sufficient attention in Indian publications, despite the enormous number of affected patients in our country. In this context it becomes relevant to be familiar with them for the comprehensive management of these patients.

Keywords: COVID-19, Neurological manifestations, Neuroimaging

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Introduction

India currently has the largest number of confirmed cases of COVID-19 in Asia and has the third highest number of confirmed cases in the world after the United States and Brazil. At the time of submission of this manuscript, the Ministry of Health and Family Welfare, Government of India confirmed a total of 27,70,000 cases, 20,40,000 recoveries and 52,889 deaths in the country due to Corona virus disease 2019 (COVID-19) pandemic. The severe acute respiratory syndrome corona virus 2 (novel coronavirus-2019; COVID-19; SARS-CoV-2) is genetically related to the original SARS-CoV that was responsible for the epidemic affecting 29 countries leaving at least 774 dead in 2002-2004 [1,2]. COVID-19 is highly contagious and was reported first in China which spread widely into more than 160 countries very rapidly. Though it affects the respiratory system predominantly, COVID-19 expresses itself as a multi system disease because

of its affinity for angiotensin converting enzyme 2 (ACE2) receptors. Single cell RNA-sequencing demonstrated the virus binding to ACE2 receptors resulting in cytokine-mediated immune response and inflammation [3]. Comorbid factors like chronic pulmonary disease, hypertension, diabetes, impaired renal function and decreased immune status exacerbate the disease. This article summarizes the published literature on Neuroimaging in patients with COVID-19 as available on the PubMed database. Reports on adults and children with neurological manifestations confirmed by neurological imaging are included in this study.

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Clinical Manifestations and Pathogenesis

Neurological symptoms are seen in many COVID-19 patients in addition to the well-known respiratory symptoms. Headache, agitation, altered sensorium, stroke, encephalitis and myalgia, brain stem dysfunction have been noted in patients with more severe COVID-19 in comparison with those having mild infection. Non pulmonary symptoms, even if as an isolated event, should be considered as an extrapulmonary manifestation of COVID-19 [4,5]. Ischemic strokes (27%), leptomeningeal enhancement (17%), and encephalitis (13%) were the most frequent neuroimaging findings. Ischemic stroke patients suffered much less from acute respiratory distress syndrome. Confusion, agitation, pathological wakefulness is predominant in this group of patients [6-9]. Intracerebral hemorrhages and acute hemorrhagic necrotizing encephalopathy have been reported as a sequel to COVID-19 infection [10]. Corona virus is virulent and invasive affecting the neuronal and glial cells by replication or autoimmune reaction. The structural similarity of SARS-CoV and MERS-CoV indicates the neurotropic nature of SARS-Cov-2 with the same pathogenesis [11]. ACE2 receptors are protective for the cerebral vasculature and SARS-CoV-2 bonds strongly to the vascular endothelium causing a leak of the virus into the brain tissue. Neuronal damage occurs even without significant inflammatory changes [12]. Neuronal, circulatory, hypoxic and immune mediated injuries are the possible mechanisms of involvement of central nervous system. ACE2, receptor for SARS-CoV-2 is highly expressed in the nasal epithelial cells [13,14]. Angiotensin II receptors are also expressed in circumventricular organs and in cerebrovascular endothelial cells, which play a role in the regulation of multiple functions in the brain, including regulation of hormone formation and sympathoadrenal system, water and sodium intake, vascular autoregulation and cerebral blood flow. In addition, a prothrombotic cascade aggravated by cytokine storm disrupts the blood–brain barrier, particularly in association with multi-organ failure [15,16]. Direct spread of SARS-CoV-2 entry into brain through the cribriform plate and olfactory bulb accessing the axonal path in a retrograde manner is another mechanism proposed as clinically evidenced by anosmia in some patients [17,18]. The relation of cerebral hemorrhages and COVID-19 infection as to a coincidence or a causal effect is speculative. However, the periventricular and endothelial distribution of ACE II receptors in abundance regulating the blood flow, hormonal, electrolyte, water and vasomotor functions in brain is an easy target for COVID-19 virus. This would explain the alteration of autoregulation and blood pressure changes leading to hemorrhages [19,20]. A systematic review and meta-analysis revealed an incidence of 2-3% of cerebrovascular accidents and altered sensorium in addition to ataxia, seizures, myalgia, headache and anosmia [21]. Early recognition of these symptoms may prevent long term complications.

Multicentric Studies & Neuroimaging Findings

T2 hyperintensities on FLAIR images predominantly in the medial temporal lobes showing different degrees of enhancement were observed in a multicentric study of patients at 16 hospitals [22]. Extensive distribution of microhemorrhages in white matter and more frequently intracerebral hemorrhage with poor prognosis were reported. The study included 37 patients having positive respiratory tract reverse transcriptase-polymerase (RT-PCR) and oxygen requirement Oval FLAIR and diffusion hyperintense lesions were noted in the corpus callosum. Multifocal hyperintense white matter lesions, non-confluent in nature showing variable enhancement with or without associated hemorrhagic lesions. The nonconfluent hemorrhagic lesions closely resembled an inflammatory demyelinating disease such as acute disseminated encephalomyelitis (ADEM) or acute hemorrhagic leukoencephalitis which needed correlation and confirmation by clinical findings and CSF analysis. Hyperintense lesions involving both middle cerebellar peduncles were demonstrated in a patient presenting with confusion. Scattered FLAIR hyperintense lesions in deep hemispheric and juxtacortical white matter were reported in another case suspected to have ADEM. Lesions showing mild diffusion restriction and contrast enhancement were also noted [23]. Pathological study demonstrated ADEM like lesions in the subcortical white matter in a patient with severe infection [24].

Extensively distributed confluent supratentorial white matter hyperintensities observed in a small group of ICU patients may be due to metabolic or toxic encephalopathy, post-hypoxic leukoencephalopathy or posterior reversible encephalopathy syndrome [25]. The two reported PRES patients had fluctuating low blood pressures possibly due to cerebral endothelial dysfunction induced by COVID-19

[26]. More vigilant blood pressure control was recommended in the patients on prolonged ventilator due to possible hypertensive encephalopathy [27].

In the largest study of neuroimaging findings in patients with COVID-19 in Italy, 15 % of a total of 725 patients showed neurological deficits [27]. Of these 108 patients MR imaging demonstrated acute infarcts in a third, intracranial hemorrhage in 6%, cerebral venous thrombosis, multiple sclerosis activity and nonspecific encephalopathy in 10-12% each. The neuroimaging features in various studies are enumerated in Table 1. In spite of no known past medical history in 31 (29 %) patients, 10 had acute ischemic infarcts and 2 had intracranial hemorrhage [Figures1, 2]. In another study, analysis of 2249 SARS-CoV-2 PCR patients identified 103 patients eligible for neuroimaging and grouped into various categories based on clinical presentations [28]. Neuroimaging did not reveal any acute findings in 36 patients. Distal small-vessel acute infarctions, lobar acute hematoma, and a basilar tip aneurysm were noted in the group of patients with mild non-focal symptoms. In the group of 25 patients presenting with stroke or transient ischemic attack, only 17 patients demonstrated acute parenchymal hematomas, small and large-vessel occlusions, acute lacunar infarctions, and small distal acute parenchymal infarctions. In this study a single patient without a past history of seizures, neuroimaging was normal while two other patients had epileptogenic lesions, encephalomalacia and cysticercosis. Imaging was negative in the majority of symptomatic patients. The authors had no definite conclusion for any strong association between neuroimaging features and COVID-19 infection [29]. In another series of 454 patients (716 studies) among 3218 patients admitted over a period of 6 weeks in NYU, neuroimaging included CT angiography of the head and neck, CT perfusion, MRI brain, MRA/MRV and MRI spine. Five patients underwent endovascular treatment of stroke following catheter angiography [30]. Ischemic stroke in 26, hemorrhagic stroke in 9, hypoxic anoxic injury in 2 and encephalitis in a single patient were noted in this cohort. Poor outcome was observed in patients with acute stroke seen on neuroimaging.

In a cohort of 64 confirmed COVID-19 patients from 10 hospitals, with neurologic manifestations, ischemic strokes (27%), leptomeningeal enhancement (17%), and encephalitis (13%) were the most frequent neuroimaging findings on MRI [Figures 3-8]. Kremer et al considered limbic encephalitis, cytotoxic lesion of the corpus callosum, radiological ADEM, radiological acute hemorrhagic necrotizing encephalopathy are possibly due to immune-mediated diseases. A potential pitfall of increased signal intensity on FLAIR images within the basal cisterns and sulcal spaces along the cerebral convexities of intubated patients having higher levels of oxygen was carefully avoided by acquiring pre-and post-contrast FLAIR sequences not to mistake for meningeal enhancement. Absence of diffuse meningeal enhancement, lesional enhancement and negative RT-PCR of the CSF samples was considered against direct effect of the virus. It was concluded that encephalitis, which is uncommon in the general population, was more frequent in this study. The pathophysiology of meningoencephalitis appears to be due

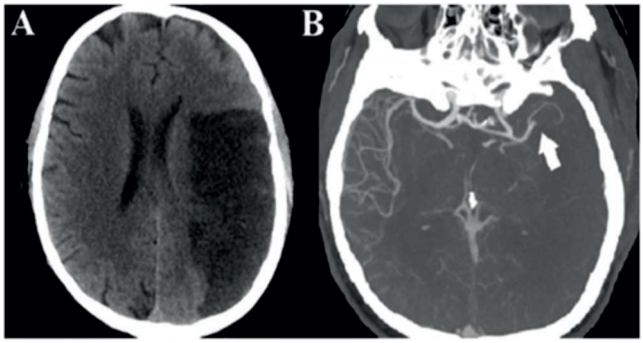

Fig. 1: A. Non-contrast CT brain in a 57-year-old male with COVID-19 shows hypoattenuation in the left MCA territory. B. CT angiography in the same patient demonstrates occlusion of the left M2 branch (arrow). There is no distal reformation. Figure reproduced with permission from Sayan Manna et al. (2020); copyright 2020 RSNA doi.org/10.1148/ryct.2020200210

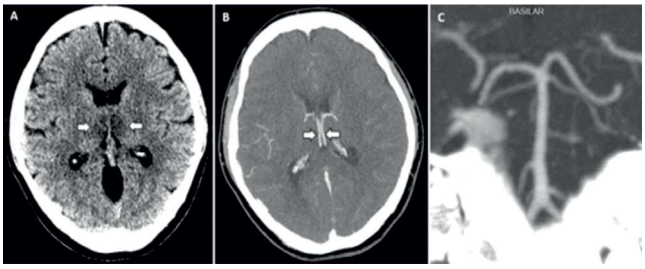

Fig. 2: (A) Unenhanced CT scan of head demonstrates symmetric low attenuation within the bilateral medial thalami (arrows).
(B) Axial CT venogram demonstrates patency of the cerebral venous vasculature, including the internal cerebral veins (arrows). Figure reproduced with permission from Neo Poyiadji et al .(2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020201187

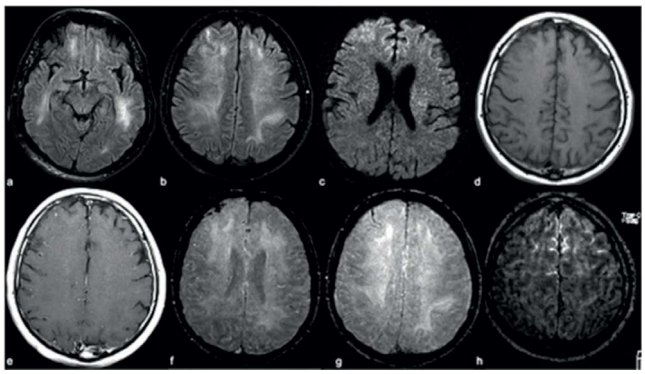

Fig. 3: Axial FLAIR images.
(A and B) demonstrate symmetric right frontal cortical hyperintensity and within frontal sulci. DWI sequence.
(C) increased signal and axial T1WI
(D) shows frontal sulcal effacement. Post-contrast
(E) shows pial-subarachnoid enhancement. SWI.
(G.) Blooming in the frontal sulci.
(H.) Depicts the bilateral leptomeningeal enhancement. Figure reproduced with permission from Kandemirli S et al (2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020201697

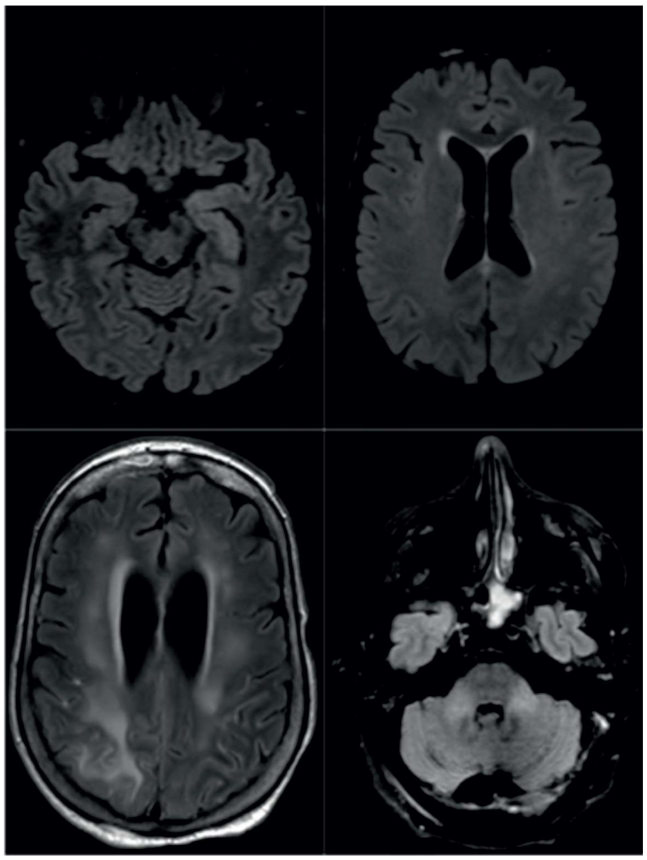

Fig. 4: Axial FLAIR in four different COVID-19 patients. (A) FLAIR hyperintensities located in the left medial temporal lobe. (B) FLAIR ovoid hyperintense lesion located in the central part of the splenium of the corpus callosum. (C) Extensive and confluent supratentorial white matter FLAIR hyperintensities (arrows). Association with leptomeningeal enhancement (stars) (D) Hyperintense lesions involving both middle cerebellar peduncles. Figure reproduced with permission from Kremer S et al . (2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020202222

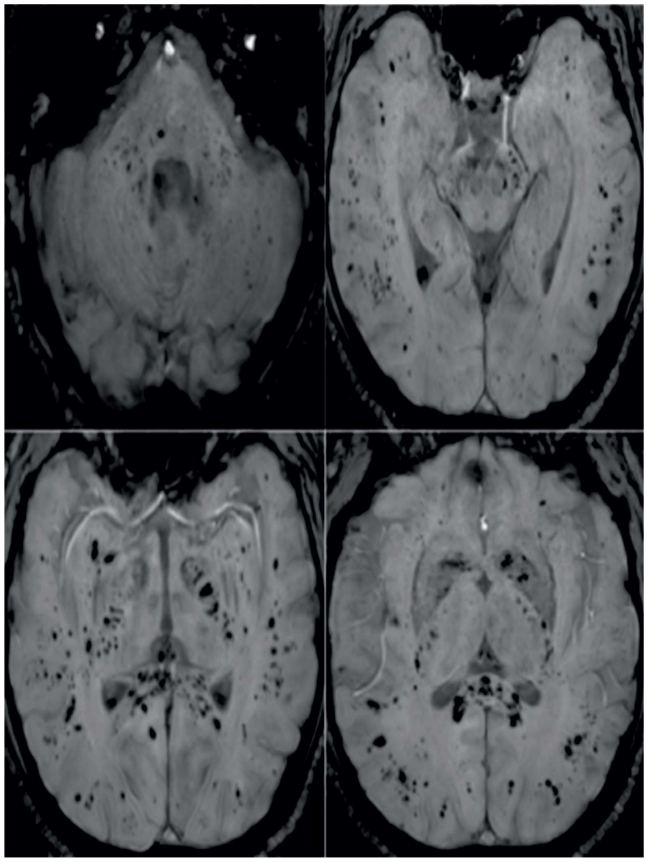

Fig. 6. 57-year old man with pathological wakefulness after sedation. Extensive and isolated white matter microhemorrhages. Axial Susceptibility weighted imaging (SWI) (A, B, C, D): multiple microhemorrhages mainly affecting the subcortical white matter, corpus callosum, internal capsule, and cerebellar peduncles. Figure reproduced with permission from Kremer S et al .(2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020202222

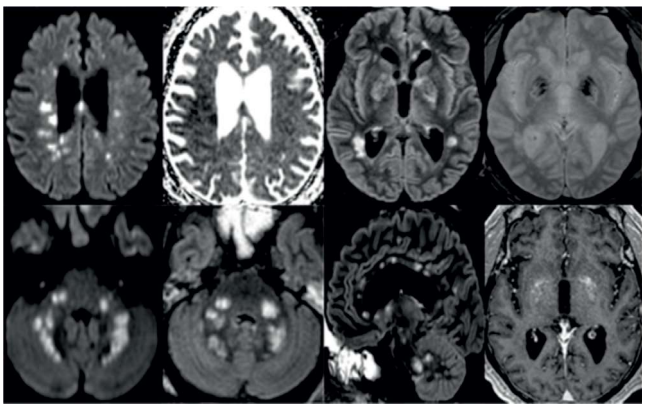

Fig. 5: 65-year-old man with pathological wakefulness. Non-confluent white matter hyperintense lesions on FLAIR and diffusion and hemorrhagic lesions. Multiple nodular hyperintense in the white matter including corpus callosum (F). Some with reduced ADC corresponding to cytotoxic edema (C). (E, G, H), with hemorrhagic changes (G), contrast enhancement. Figure reproduced with permission from Kremer S et al. (2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020202222

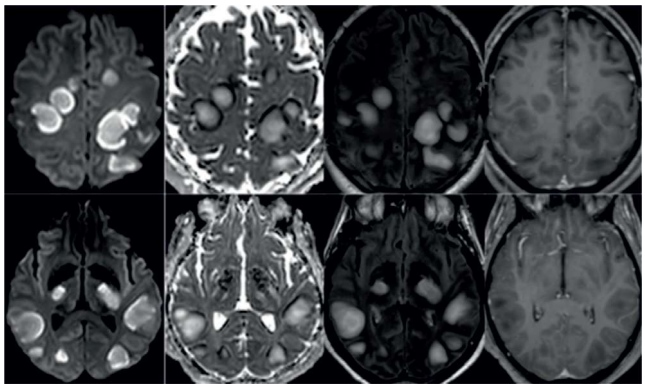

Fig. 7. 54-year old man with pathological wakefulness after sedation. Non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion, with variable enhancement. Multiple nodular hyperintense Diffusion and FLAIR subcortical and corticospinal tracts lesions. Elevated ADC corresponds to vasogenic edema and a ring of reduced ADC corresponds to cytotoxic edema (C, D). Mild enhancement is detected (G, H). Figure reproduced with permission from Kremer S et al .(2020) copyright 2020 RSNA. doi.org/10.1148/radiol.2020202222

Table 1: Number of patients for neuroimaging and imaging features are shown.

Author	Total no. of patients	Imaging	Imaging findings
Rajan Jain et al. (2020) [30]	3218	454 patients Neuroimaging (716 studies CT, CTA, CT Perfusion, MRI, MRA/MRV/MRI Spine) 38 (8.4%) positive 416 (91.6%) Negative	Large infarct 17 (44.5%) Lacunar infarct 9 (24%) Hemorrhagic Stroke 9 (24 %) Encephalitis 1 (2.5%) Hypoxic ischemia 2 (5%)
Abdelkader M et al., (2020) [28]	725	108 patients MRI – 20 MRI Spine 3 CT – 107	Large vessel infarcts – 19 Small v. infarcts – 11 Cardioembolic – 3 Hypoxic-ischemic encephalopathy – 1 I.C hemorrhages – 12 PRES – 1 Cranial Nerve enhancement - 1 MS Exacerbation – 2 T2/FLAIR Hyperinrtensity - 12 Venous Thrombosis- 2
A. Pons-Escoda et al (2020) [29]	2249	103 patients MRI in 16 patients. (71 CT 16 CT + CTA 1 MRI 6 MRI + CT 9 MRI +CT + CTA)	Large vessel stroke 2 Small vessel strike 4 Hematoma 4 Aneurysm 1 Metastasis 2 Normal 3
Stefanos Klironomos et al. (2020) [38]	185	MRI – 47 DSC - 19 CT – 222 MRI Spine - 7	Leukoencephalopathy - 44% Leptomeningeal enhancement Regression on follow-up
Anna Rita Egbert et al. (2020) [39]	26 Published articles	MRI - 361	White matter hyperintensities- 53% Infarcts & hemorrhages Microhemorrhages
Sanaz Katal et al. (2020) [40]	Meta analysis of 28 studies.	116 Eligible Patients MRI - 90 cases.	Normal 37 (41%) Hemorrhage - 7 Hemorrhagic PRES - 2 Vascular Thrombosis - 14 (12 arterial & 2 venous) Cortical FLAIR signal abnormality - 10 Hypoperfusion, leptomeningeal enhancement - 10 Acute stroke - 6 ANE, ADEM - 2 each Meningitis / Encephalitis - 2
Stéphane Kremer et al. (2020) [8]	Study at 10 French Centers	64 eligible patients MRI	Abnormal - 36 (56%) Ischemic strokes - (27%) LME & encephalitis - (13%) Total encephalitis - 8 Limbic encephalitis - 2 Acute hemorrhagic necrotizing encephalopathy - 2 Miscellaneous encephalitis - 2 ADEM & CLOCC – 1 case each.
Kandemirli et al. (2020) [25]	749	MRI in 27 of 50 symptomatic patients	Normal - 15 (56%) Cortical FLAIR signal abnormality - 10 Diffusion restriction - 7 LME - 5 Punctate cortical blooming - 3 Subcortical & deep WM signal FLAIR abnormality - 6 Tranverse sinus thrombosis 1
S Kremer et al. (2020) [22]	190	MRI in 37 patients	FLAIR/Diffusion hyperintensities in medial temporal lobe UNILATERAL - 16(43%) Non-confluent WM hyperintensirties with hemorrhages - 11 (30%) Extensive hemorrhages - 9 (24%) Confluent WM Hyperintensities - 4 (11%) FLAIR/DWI Ovoid Hyperintensities in Corpus Callosum -2 (5%) Non-confluent multifocal WM hyperintesities with enhancement. 2 (5%) ANE - 2 (5%) Middle Cerebellar peduncles hyperintensities - 2 (5%).
Timothy Parsons et al. (2020) [23]	1	1 Patient ADEM.	Hyperintense lesions on FLAIR in deep hemispheric and juxtacortical white matter. DWI restricted diffusion on the indicating acuity, but not consistent with infarction. FLAIR hyperintensity in the left frontal juxtacortical white matter. Mild enhancement. Small intraventricular hemorrhage GRE - No hemorrhages.
Kishfy L, et al. (2020) [26]	2	2 Patients PRES	Hyperintensity of subcortical white matter of occipital lobes and posterior temporal lobes Effacement of the adjacent sulci MRI (SWI) & CT Brain - convexal subarachnoid hemorrhage Diffusion weighted imaging (DWI) and T1 post-contrast imaging were unremarkable

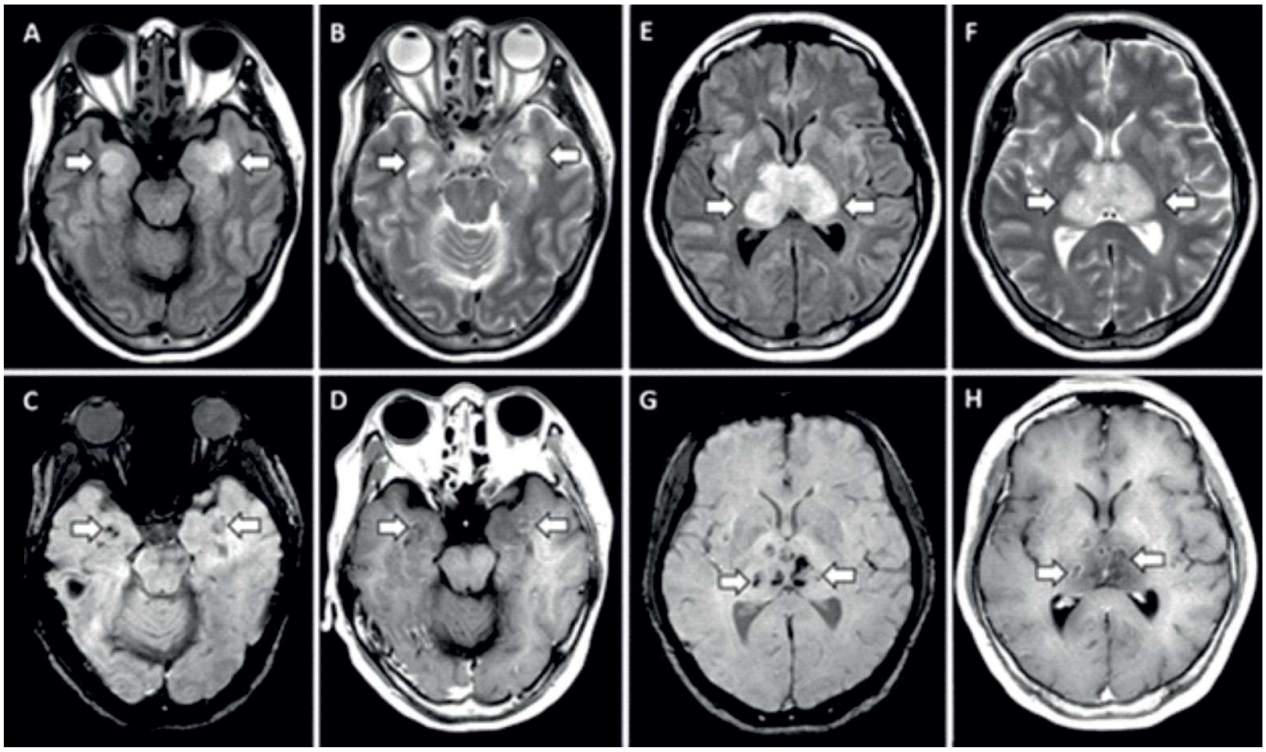

Fig. 8. (A, B, E, F) T2-weighted fluid-attenuated inversion recovery MRI scans demonstrate hyperintensity within the bilateral medial temporal lobes and thalami (arrows), with evidence of hemorrhage indicated by, *C, G,* hypointense signal (arrows) on susceptibility-weighted images and, *D, H,* rim enhancement (arrows) on contrast material–enhanced images. Figure reproduced with permission from Neo Poyiadji et al .(2020); copyright 2020 RSNA. doi.org/10.1148/radiol.2020201187

to immune and/or inflammatory processes in cerebrospinal fluid though the virus is seldom demonstrated in cerebrospinal fluid [31]. In a study of 214 patients from 3 centers in China, though 78 patients with neurological symptoms had tested positive for COVID-19, neuroimaging and diagnostic procedures such as lumbar puncture and electromyography/nerve conduction velocity were intentionally not performed to avoid the risk of cross infection. In these patients it was uncertain whether the neurological manifestations were caused by the virus directly or by the underlying pulmonary COVID-19. However, severity of neurological impairment was proportional to the severity of the respiratory infection with a rapid downhill of the clinical course [32].

Fatal acute necrotizing encephalitis (ANE) in isolation or associated with myocarditis was reported sporadically. ANE is related to intracranial cytokine storms resulting in blood brain barrier breakdown but without viral invasion or demyelination [33,34]. In the reported patient brain MRI revealed bilateral rim enhancement of thalami, occipital leptomeningeal enhancement and hemorrhages in cerebellum. Cardiac MRI showing diffuse myocardial signal hyperintensity in both ventricles and pericarditis was reported Invariably symmetric, multifocal lesions with thalamic involvement are characteristically seen in ANE. MRI shows T2-weighted fluid-attenuated inversion recovery hyperintense signals with internal hemorrhage evidenced by hypointensities on susceptibility-weighted images. CT images reveal hypoattenuating lesions. Brainstem, cerebral white matter and cerebellum may be also involved. Thromboembolic events in relation to COVID-19 have been increasingly reported. Three patients in the fourth decade presented with confirmed (SARS-CoV-2) infection showing MRI features of venous thrombosis involving both the superficial and deep systems. The deep system involvement was in straight sinus and vein of Galen in one patient, internal cerebral veins in a second patient and deep medullary veins in the third [35]. Extensive bilateral subcortical and deep white matter lesions were non-enhancing with restricted diffusion. Gradient recalled-echo images revealed multiple susceptibility artifacts consistent with petechial hemorrhage. ANE was not considered in the absence of deep ganglia involvement. Diffuse generalized hypo intensity of the white matter on T2- and T2*-weighted images may be seen in disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and related thrombotic microangiopathies, including thrombosis of the deep medullary veins. There were no large-vessel occlusions or deep MCA ischemia or infarction in these patients. D-dimer, fibrin/fibrinogen-degradation products, and fibrinogen were significantly increased in many patients [36]. Positive antiphospholipid antibodies were demonstrated in 3 patients with critical COVID-19 and

multifocal ischemic strokes [37]. Anticardiolipin immunoglobulin A and anti–b 2-glycoprotein I immunoglobulin A and immunoglobulin G may play a role in both arterial and venous infarcts Monitoring of these biochemical inflammatory markers is necessary for early recognition of severity of the disease. Neuroimaging of 185 patients with positive for rt-PCR at Karolinska University Hospital over a period of 10 weeks included 222 brain CT, 47 brain MRI and 7 spinal MRI scans. The most common findings were ovoid shaped intra-axial susceptibility abnormalities predominantly in corpus callosum and juxtacortical areas. Dynamic susceptibility contrast perfusion MRI in 19 patients did not reveal any abnormality. Leukoencephalopathy (44%) was noted in many patients besides leptomeningeal, cranial nerve and spinal nerve enhancement in few patients. MRI follow-up demonstrated regression of leukoencephalopathy and progressive leptomeningeal enhancement [38].

A systematic literature search, review and data analysis of 26 published articles including 361 patients undergoing MRI examinations, reported hyperintense signals in the white matter in 53% patients, microhemorrhages, infarcts and larger hemorrhages. Half of these abnormalities were seen in the anterior and posterior white matter. The authors attributed these abnormalities to leukoencephalopathy, leukoaraiosis or rare field white matter [39]. Katal S et al in their systematic review found that in around 41% of 90 cases with COVID-19 infection and neurological signs, there was no acute abnormalities in brain imaging. In the remaining 53 patients, 14 patients had vascular thrombosis either of the artery or vein, seven had hemorrhage, 10 had cortical FLAIR abnormality. Few patients had leptomeningeal enhancement [40]. In their case series of 4 patients, Nicholson et al. reported thrombotic microangiopathy showing multifocal subcortical/ cortical petechial type hemorrhages, more prominent in the susceptibility weighted images [41]. In a case series of patients with persistent headache and anosmia, imaging of the olfactory bulb showed microbleeding or abnormal enhancement. Qualitative or subjective analysis of a small structure such as the olfactory bulb is difficult and a quantitative evaluation of T2/FLAIR signal intensity ratio with the adjacent white matter in the loss of smell and in anosmic groups revealed a statistically higher ratio in the anosmic group. The authors suggest that this could be due to the virus-related inflammatory reaction arising in the neuroepithelium of the olfactory cleft impairing the olfactory neural or sustentacullar cells, and hence the olfactory cleft edema. A coronal thin slice pre- and/or post gadolinium fat-suppressed T1WI sequence of the anterior cranial fossa while doing MRI brain in patients having headache and anosmia [42].

Studies in Pediatric Population

In a pediatric population of 50 children confirmed to be having SARS--COVID-2 - children presented with headaches, brainstem signs, meningism, encephalopathy and cerebellar ataxia. All had roximal muscle weakness and decreased reflexes. On MR imaging, transient reversible T2-hyperintense lesions and restricted diffusion were observed in the splenium of corpus callosum in all 4 children. Genu and centrum semiovale on both sides were involved in two patients [43]. Splenial lesions are also noted in severe electrolyte disturbances, ischemia, lymphoma and PRES. Transient lesion in the splenium was also described in children with Kawasaki disease. In another report, unilateral focal vasculopathy as focal irregular narrowing of the proximal left middle cerebral artery with acute infarcts in the left basal ganglia and insula were demonstrated in a 12 year child who tested positive for SARS-CoV2 presenting with seizures, right hemiparesis and dysarthria [44]. COVID-2 related focal arteriopathy was considered more likely than embolic stroke and dissection because of lack of thrombotic processes outside the CNS [Figure 9].

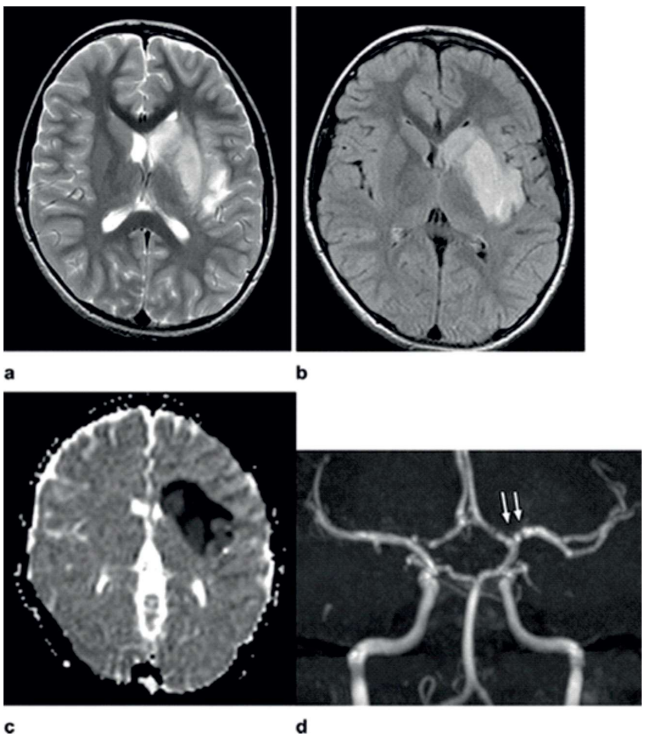

Fig. 9. Axial T2-weighted (A,B) and FLAIR, DWI (C) Magnetic resonance imaging show diffuse hyperintense signal and edema of the caudate nucleus head, putamen, anterior limb of the internal capsule, and parts of external capsule and insula on the left side, in keeping with an acute infarct. D. MR angiography demonstrates focal irregular narrowing the proximal left M1 segment of the middle cerebral artery. Figure reproduced with permission from Mirzaee et al .(2020); copyright 2020 RSNA. *doi.org/10.1148/radiol.2020202197*

Advanced Neuroimaging

In a state-of-the-art study, first of its kind, of cerebral microstructural changes in patients recovering from COVID-19, voxel-based morphometry and diffusion tensor imaging metrics were used to determine the regional volumes based on diffusion tensor imaging (DTI) and 3D high-resolution T1WI sequences. Bilateral gray matter volumes were significantly higher in olfactory cortices, hippocampi, insular cortices, left Rolandic operculum, left Heschl's gyrus and right cingulate gyrus [45]. Statistically significant reduction of diffusivity and increase of fractional anisotropy in white matter, axial diffusivity in the right corona radiata and external capsule were observed when compared with non-COVID-19 volunteers. Global gray matter volumes of left Rolandic operculum, left Heschl's gyrus, right cingulate, bilateral hippocampi and global mean diffusivity of white matter correlated with memory loss. Gray matter volumes of the right cingulate gyrus and left hippocampus were related to loss of smell. The diffusivity scores and gray matter volumes correlated with lactate dehydrogenase levels in their patients. Volumetric changes of the central olfactory cortices and micro-structural abnormalities in partial right hemispheric white matter were demonstrated as new evidence in this study. Disseminated intravascular coagulation, vasogenic oedema predominantly in posterior regions, effects of cytokines on the endothelium and virus-induced endothelial dysfunction were the possible mechanisms to explain the morphological changes triggering the widespread "Endothelitis". The study did not find any brainstem abnormalities despite presenting with the profound respiratory distress.

Imaging Diagnosis and Differentials

It may be noted that a few of the neuroimaging findings seen in COVID-19 patients such as encephalitis, hemorrhages and reversible leukoencephalopathy are seen in other viral infections. However, the association of vascular thrombosis appears to be more common with COVID-19. Since viral infections such as Dengue and Japanese encephalitis are quite common in some parts of the country, it is essential to keep these possibilities as well in the differential diagnosis during clinical work up of patients with similar neuroimaging findings. In spite of the huge number of patients affected in India, the neuroimaging features in COVID-19 infection has hardly been reported. The authors were unable to find reported Indian literature on neuroimaging findings of similar reports from Europe, North America and China. In India patients undergo imaging using X ray and CT for evaluating pulmonary findings. There is reluctance for performing MRI examinations in COVID positive patients due to risk of contamination of the often only available single MRI machine and the logistics of its sanitization in most hospitals in the country. Due to the disease severity and especially if the patient is restless or on life supporting systems, a shorter imaging technique or alternately CT study is preferred.

Conclusion

Ischemic and hemorrhagic cerebrovascular events are the most common neuroimaging abnormalities in COVID-19 patients, though 40% of the studies are normal. Isolated cases of encephalitis, meningitis, and demyelination are reported in the literature as parenchymal involvement of the brain. Signal intensity and volume changes of olfactory bulb and involvement of splenium of corpus callosum are demonstrated in a subset of the patients. Awareness of the unexplained neurologic symptoms and imaging features in association with COVID-19 infection is essential in the current pandemic. Follow up by clinical assessment and imaging is helpful to evaluate prognosis of these patients. Severity of the illness and the risk for spread of infection are definite constraints for routine neuroimaging of these patients who are often on life supporting systems.

Acknowledgements

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Fig. 1: Manna S, Wruble J, Maron SZ, Toussie D, Voutsinas N, Finkelstein M et al. COVID-19: A Multimodality Review of Radiologic Techniques, Clinical Utility, and Imaging Features. Radiol Cardiothorac Imaging. 2020 Jun 1;2(3):e200210. doi: 10.1148/ryct.2020200210.

Figs. 2 & 8: Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology. 2020 Aug;296(2):E119-E120. doi: 10.1148/radiol.2020201187.

Fig. 3: Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. Radiology. 2020 Oct;297(1):E232-E235. doi: 10.1148/radiol.2020201697.

Figs. 4-7: Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology. 2020 Nov;297(2):E242-E251. doi: 10.1148/radiol.2020202222.

Fig. 9: Mirzaee SMM, Gonçalves FG, Mohammadifard M, Tavakoli SM, Vossough A. Focal Cerebral Arteriopathy in a Pediatric Patient with COVID-19. Radiology. 2020 Nov;297(2):E274-E275. doi: 10.1148/radiol.2020202197.

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