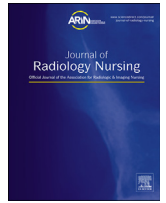




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Role of Neuroimaging in COVID 19 Infection—A Retrospective Study



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A B S T R A C T

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the family of coronaviruses, induces COVID-19 disease which is predominantly a respiratory illness. Several authors have reported neurological manifestations such as acute venous and arterial strokes and rarely acute disseminated encephalomyelitis, hemorrhagic posterior reversible encephalopathy syndrome, and acute inflammatory demyelinating polyneuropathy by studying magnetic resonance imaging of brain parenchymal signal abnormalities in patients with COVID-19. Owing to sparsity of literature on extrapulmonary manifestation of COVID, it is imperative to study the mechanism of neuronal invasion and manifestations of COVID-19. This study aimed to assess and correlate neurological manifestations in patients with COVID using imaging findings on computed tomography and magnetic resonance images. A retrospective observational study was conducted among 80 patients who tested positive for COVID-19 disease via a reverse transcription–polymerase chain reaction (RT-PCR) test in a tertiary care teaching institute in Pimpri, India. Most patients presented with acute arterial and venous strokes. Arterial stroke was the most prevalent finding; nearly 42.50% showed imaging findings consistent with arterial stroke; 25% patients had findings of venous stroke. Meningitis and spontaneous hemorrhage were found in 10% of cases. Rare complications such as acute disseminated encephalomyelitis comprised 7.50%, and encephalitis was found in 5%. This study highlights the need for increased neuroimaging in suspected patients to alert the treating physicians about the neurological complications. As the conventional RT-PCR and serum tests are unremarkable in the early onset of COVID-19, it is important to have a multidisciplinary approach and more neurology consultations in COVID-19 suspected patients with an emphasis on prompt neuroimaging to prevent potential life-threatening complications. To alert the attending physician about neurological involvement in patients with COVID-19, it is vital that nursing staff is aware about the neurological manifestations of COVID-19 so that they can recognize change in patients' neurological status without any undue time delay.

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Introduction

The outbreak of coronavirus has recently become a global threat (Zheng et al., 2020). Coronavirus gets its name from its appearance that resembles solar corona owing to its long surface spikes (Zu et al., 2020). It is an enveloped sRNA virus (Zu et al., 2020). The

viral genome on the envelope encodes four major structural proteins. The spike protein (S) is the one responsible for entry of the virus into a host cell. It acts by binding to an angiotensin-converting enzyme 2 receptor (ACE2-R) and mediates subsequent fusion between the envelope and host cell membranes (Kirchdoerfer et al., 2016; Xu et al., 2020).

SARS-CoV-2, a member of the family of coronaviruses, induces the COVID-19 disease which is predominantly a respiratory illness. Most patients present with dry cough, fever, sore throat, myalgia, arthralgia, and headache. Patients with more severe symptoms present with breathlessness and often require invasive ventilation (Behzad et al., 2020).

However, it has been observed that there have been associated extrapulmonary manifestations in a number of patients, such as neurological manifestations, gastrointestinal findings (acute

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abdomen), liver dysfunction, circulatory instability, and hematologic complications (Behzad et al., 2020).

Several authors have reported neurological manifestations such as acute venous and arterial strokes and rarely acute disseminated encephalomyelitis, hemorrhagic posterior reversible encephalopathy syndrome, and acute inflammatory demyelinating polyneuropathy by studying MRI brain parenchymal signal abnormalities in patients with COVID-19 (Kremer et al., 2020).

Owing to sparsity of literature on extrapulmonary, more specifically neurological manifestation of, COVID-19 pneumonia, it is imperative to study the mechanism of neuronal invasion and manifestations of COVID-19.

Therefore, the present study was conducted to assess and correlate neurological manifestations in patients with COVID-19 using imaging findings on computed tomography (CT) and magnetic resonance (MR) images.

Material and methods

This was a retrospective observational study conducted among 80 patients who tested positive for the COVID-19 disease via reverse transcription polymerase chain reaction (RT-PCR) test in a tertiary care teaching institute in Pimpri, Pune (India). Patients who had undergone high-resolution computed tomography chest with characteristic peripheral basal ground glass opacities and presented with symptoms such as sudden onset limb weakness, aphasia, loss of consciousness, disorientation, and throbbing headache were included. This was correlated with a positive RT-PCR test for SARS-CoV-2 antigen. Approval from the ethics committee was obtained before commencement of this study.

Observations and Discussion

Our study was a retrospective observational study that was conducted to identify the emerging neurological manifestations of COVID-19 to aid in prompt patient management and in turn reduce mortality associated with it.

The timely diagnosis of COVID-19 infection poses a hurdle that many physicians have failed to cross.

As per the study conducted by Desforges et al., it has been confirmed that Human coronaviruses are neurovirulent and are responsible for causing various neurological deficits such as acute disseminated encephalomyelitis (ADEM), venous thrombosis, and so forth (Kato & Laure, 2020) (Desforges et al., 2020).

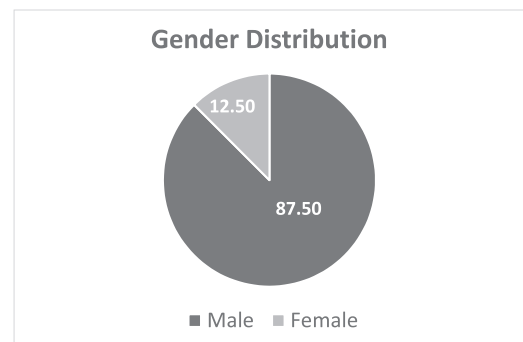
Similar to SARS-CoV, SARS-CoV-2 infiltrates the intracellular space by acting on ACE2-R. COVID-19 may invade the central nervous system either directly via the cribriform plate or by the hematogenous route. Glial cells and neurons in the brain express ACE2-R and, hence, are targeted by COVID-19 (Zheng et al., 2020) (Wang et al., 2020).

Although reverse transcriptase PCR test is considered the gold standard, it has been known to give false negative results in the early onset of COVID-19 (Oliveira et al., 2020). Time is essential when it comes to promptly treating COVID-19 to prevent neurological complications such as venous sinus thrombosis and arterial strokes. The average time taken for RT-PCR test results is anywhere between 3 hours and 12 hours (Esbin et al., 2020). The initial serum tests such as complete blood cell count, metabolic panel, urine studies, and inflammatory markers (sedimentation rate, C-reactive protein level) are unremarkable (Utukuri et al., 2020). Cerebrospinal fluid studies in most cases are unequivocal. However, later in the course of the disease, higher erythrocyte sedimentation rate, white blood cell numbers, and increased levels of plasma proinflammatory cytokines and D-dimer are observed (Rothan &

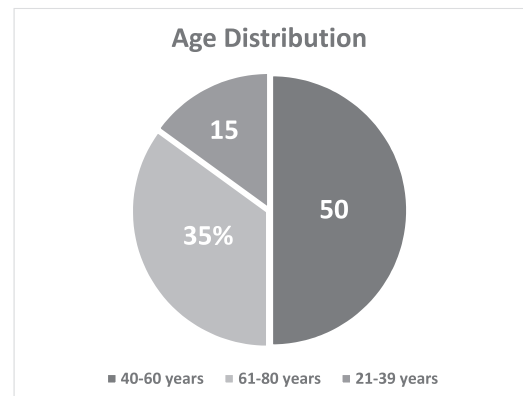
Byrareddy, 2020). As these biochemical changes take a long time to appear, the burden of prompt diagnosis falls on imaging investigations, especially CT brain. The short time to diagnosis and noninvasive natures of CT and MR imaging techniques give it an upper hand in the likely prevention of life-threatening complications of COVID-19 neuroinvasion.

A total of 80 adult patients were included in this study. Diagnosis of COVID-19 was made based on a detection of SARS-CoV-2 by RT-PCR assays on the nasopharyngeal, throat, or lower respiratory tract swabs. Patients showing neurologic manifestations such as sudden-onset limb weakness, aphasia, loss of consciousness, disorientation, throbbing headache, or abnormal brain CT/MRI with acute/subacute abnormalities were included.

Demographics



Graph 1. Gender—The majority of the subjects were male at 87.5% (70), and females constituted 12.5%.

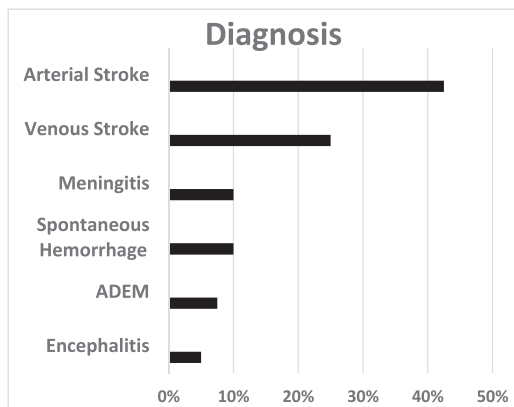


Graph 2. Age—Mean age of the subjects in the study was 54.16 (SD: 13.57). The median age was 55 years with an age range of 26 years to 80 years. The majority of the patients were between 40 and 60 years of age (40 [50%]), followed by 61-80 years (28 [35%]), and 21-39 years (12 [15%]).

Evaluation of symptoms

The mean duration of neurological symptoms was 2.91 days with an SD of 1.58. All the patients had nonspecific respiratory symptoms for an average of 5 to 7 days.

Sudden-onset limb weakness was the most common presenting complaint in 57.50%, followed by throbbing headache in 17.50%, and loss of consciousness and aphasia in 12.5% each.



Graph 3. Diagnosis.

A vast majority of patients presented with acute arterial and venous strokes. Arterial stroke was the most prevalent finding; nearly 42.5% (34 patients) showed CT and MR imaging findings consistent with arterial stroke, and 25% (20 patients) had findings of venous stroke. Meningitis and spontaneous hemorrhage were each diagnosed in 10% (8 patients) of cases. The rare complications such as acute disseminated encephalomyelitis comprised 7.5% (6 patients) each, and encephalitis (4 patients) was found in the remaining 5%.

Imaging findings

Ischemic Stroke

A study conducted by Semenov et al. in 2011 (Semenov et al., 2011) compared imaging findings of arterial and venous strokes and hypothesized certain factors that can be used universally for the accurate diagnosis of arterial and venous strokes. They studied the imaging differences under three characteristic findings, first being localization of the lesion; second, presence of vascular edema; and third, association of the lesion with hemorrhagic changes. They evaluated that early MR signal characteristics and appearance of brain substance in CT could not reliably differentiate the nature of the pathology (arterial or venous).

On subsequent imaging, it was noted that venous infarcts were localized in the parieto-occipital, occipital, and corpus callosal areas, which were rarely affected in arterial strokes. Arterial strokes were distributed in the area of circle of Willis arterial territories.

Another differentiating factor put forth by Semenov et al. (Semenov et al., 2011) was the early onset of severe vascular edema in case of venous infarction.

The third factor described by Semenov et al. (Semenov et al., 2011) was the high frequency of hemorrhagic transformation (as high as 63% in their study) as an indicator of a venous infarct compared to an arterial lesion.

Arterial Stroke

Most patients presented with sudden-onset upper or lower limb weakness associated with facial asymmetry and slurring of speech.

Initial CT head revealed ill-defined hypodensity in affected cortical/subcortical regions with effacement of the adjacent sulci.

On MR imaging, coronal fluid attenuation inversion recovery (FLAIR) hyperintense areas were noted involving the affected areas, which, in our study, were most commonly bilateral gangliocapsular regions, showing diffusion restriction with corresponding low apparent diffusion coefficient (ADC) values and no blooming on gradient echo sequences. Some patients showed loss of flow voids along the affected major intracranial vessels in the form of intraluminal T2/FLAIR hyperintensity. On performing MR angiography, loss of flow signal was seen in the affected intracranial vessels (Figure 1).

Venous Stroke

Most patients presented with generalized headache for 1 week, with acute increase in severity of pain and, in some cases, associated with visual auditory disturbances and photophobia.

Noncontrast CT, when not associated with venous hemorrhage or infarction, showed hyperdensity of the affected sinus. Thrombosis appeared as a hyperdensity along cortical veins or cortical sulci. When associated with hemorrhagic transformation, the CT findings were intracerebral, multilobulated, and gyriform hyperdensity/hemorrhagic lesions involving the affected cortical and subcortical distribution with hyperdensity of the affected sinus and the deep brain veins. Presence of extensive hypodense vasogenic edema was also characteristically found.

Most frequently encountered MR findings were areas of blooming on gradient echo sequences seen in affected parietal-occipital region, very often parasagittal in location, with associated hyperintensity on FLAIR, T1W images and heterogeneous appearance on T2W images. T2 hyperintense perilesional edema

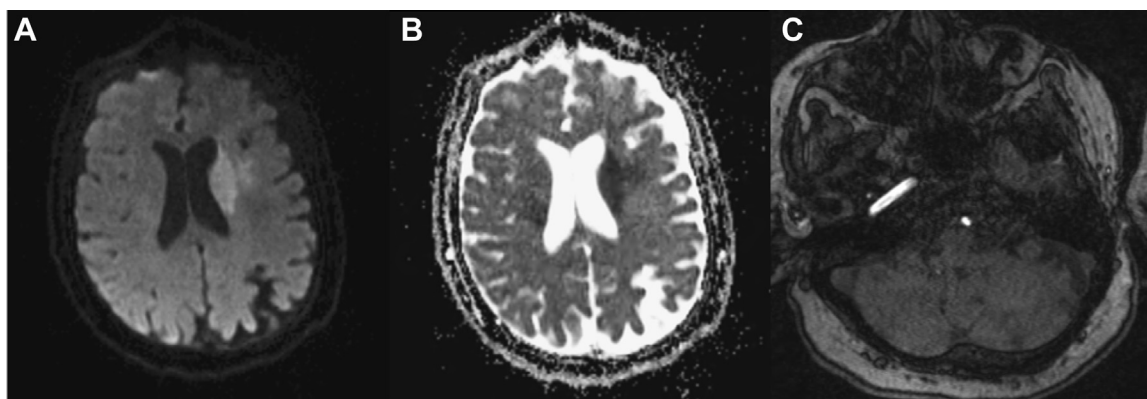


Figure 1. A 50-year-old male complaining of fever and sudden-onset right-sided limb weakness; RT-PCR positive for COVID-19. The left internal capsule, left putamen, left insular cortex, left caudate nucleus, and left corona radiata showed hyperintense areas on FLAIR images with diffusion restriction. (A) FLAIR sequence magnetic resonance image; axial section, with corresponding low ADC values, (B) Apparent diffusion coefficient (ADC) map, and no GRE blooming indicative of acute nonhemorrhagic infarction. No flow, indicative of thrombosis, is seen in left interpetrous and intracranial ICA and MCA, (C) MR angiography.

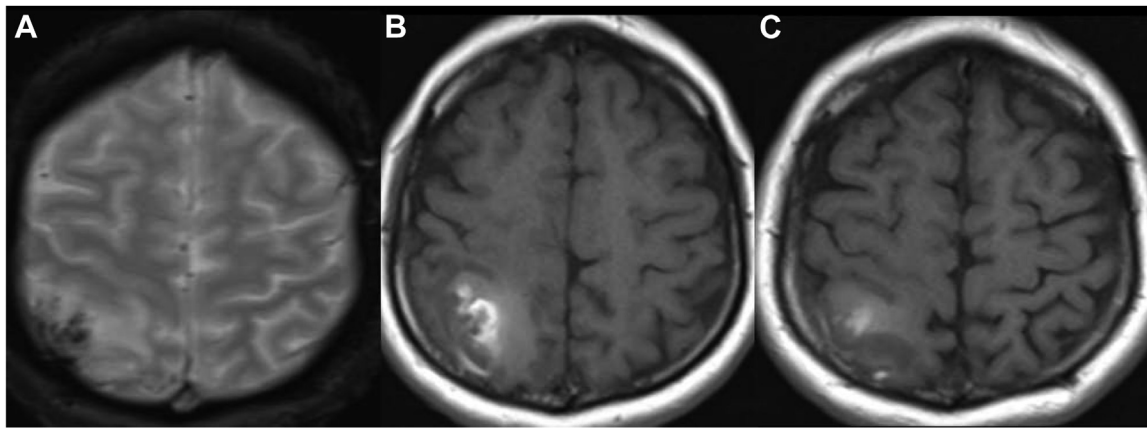


Figure 2. A 53-year-old male complaining of fever and throbbing headache; RT-PCR positive. In the right high parietal zone, the parasagittal region shows the area of GRE blooming. (A) gradient recalled echo sequence—magnetic resonance imaging; on FLAIR and T1W images, it appeared hyperintense with the adjacent superficial cortical vein showing hyperintensity on T1W images—which was suggestive of thrombosis. (B) FLAIR and (C) T1 MR images. It appeared heterogeneous on T2W images. Perilesional edema was seen along with mass effect in the form of effacement of adjacent sulci.

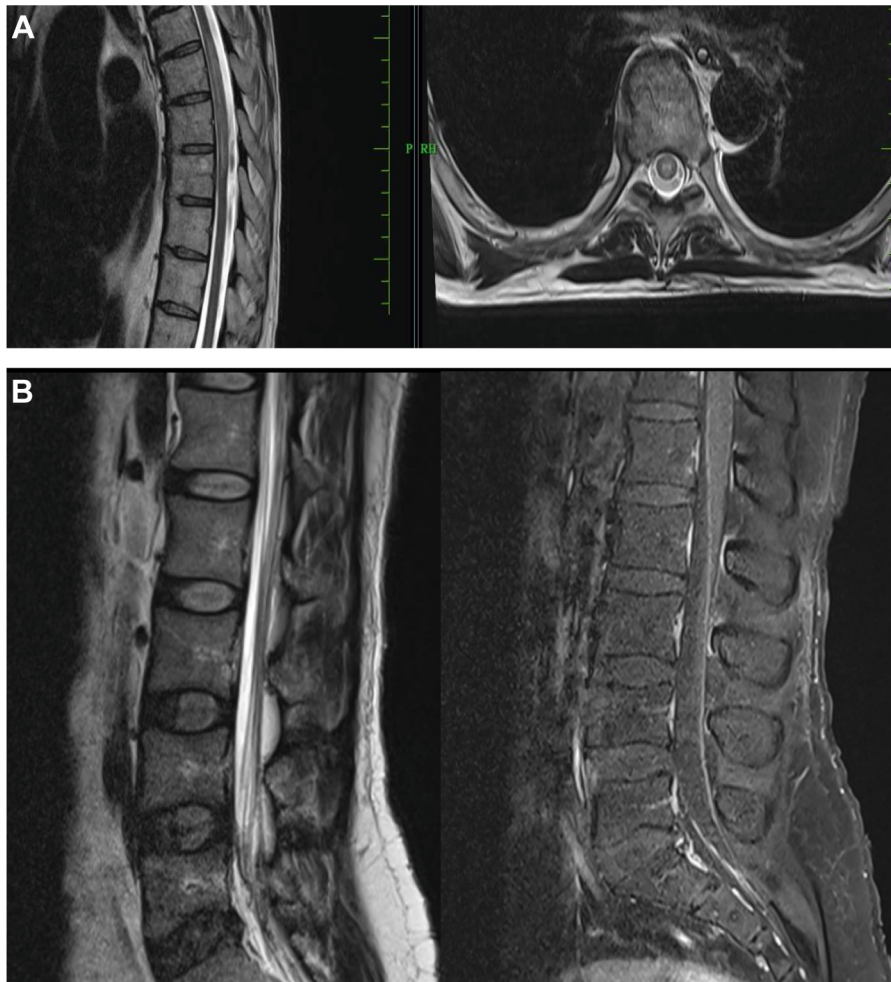


Figure 3. A 42-year-old male complaining of cough and bilateral lower limb weakness with associated tingling sensation; RT-PCR positive. (A) T2-weighted magnetic resonance images in sagittal and axial sections—dorsal spine. In the dorsal spine cord, there are diffuse T2 hyperintense signals affecting more than two-third of the spinal cord circumference. There is mild swelling of the spinal cord, with subarachnoid gaps being effaced. (B) T2 and T1+contrast-enhanced magnetic resonance images in sagittal sections—lumbar spine on the surface of the spinal cord, conus medullaris, and even along the filum terminale, diffuse irregular meningeal enhancement was noted.

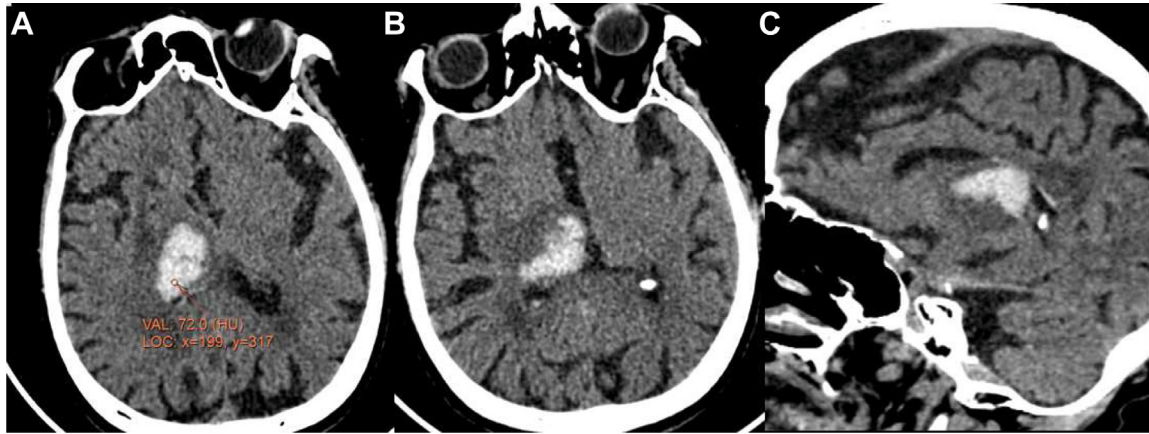


Figure 4. A 61-year-old male complaining of fever and dry cough with sudden-onset disorientation and upper and lower limb weakness; RT-PCR positive. An ill-defined hyper density of approx. size $33 \times 26 \times 24$ mm (AP \times CC \times T) (CT HU: 72) was noted in the right thalamus. (A and B) Plain computed tomography axial section and (C) sagittal section, with hypodense edema surrounding it, was indicative of intraparenchymal bleeding. A mass effect was noted in the form of effacement of the right lateral ventricle and third ventricle.

was also noted. Adjacent superficial cortical vein shows hyperintensity on T1W images—suggestive of thrombosis.

MR venography was performed to confirm the aforementioned findings. It was consistent with corresponding loss of signal flow in affected major sinuses and cortical veins in most cases (Figure 2).

Meningitis with Transverse Myelitis

Eight patients presented with bilateral weakness of lower limbs with tingling sensation below the umbilicus associated with restriction of movement for 8 days and fever for 10 – 15 days.

MRI brain and lumbar spine with contrast was performed in all of them.

Subtle sulcal hyperintensity on FLAIR images was noted in parafalcine parietal-occipital regions with effacement of sulci. There was abnormal meningeal enhancement noted in the basilar cisterns, mainly in the perimesencephalic prepontine and cerebellopontine angle (CPA) cisterns, the bilateral sylvian fissures, bilateral cerebral sulci, and along the brainstem surface and cerebellar sulci, folia, and fissures. These changes are better appreciated on postcontrast FLAIR images.

MR lumbar spine showed diffuse T2 hyperintense signals in the dorsal spine cord and in conus medullaris with mild swelling of the spinal cord and effacement of subarachnoid spaces, consistent with findings of transverse myelitis (Figure 3).

Spontaneous Hemorrhage

Eight patients presented with sudden-onset disorientation and upper and lower limb weakness. There was associated fever and dry cough for 3 days. On further investigations, these patients did not provide a history of comorbidities, especially hypertension.

CT brain performed in these patients showed ill-defined extensive hyperdense areas, consistent with the Hounsfield Units (HU) value of hemorrhage. There was associated intraventricular and subarachnoid extension of hemorrhage.

MRI was not performed in these patients as the diagnosis was evident on CT imaging (Figure 4).

Acute Disseminated Encephalomyelitis

As per previous studies, ADEM is a rare complication of COVID-19 infection. It commonly presents in children, with a history of recent vaccination or a respiratory infection (Utukuri et al., 2020). However, the patients presented to our facility were adults, and

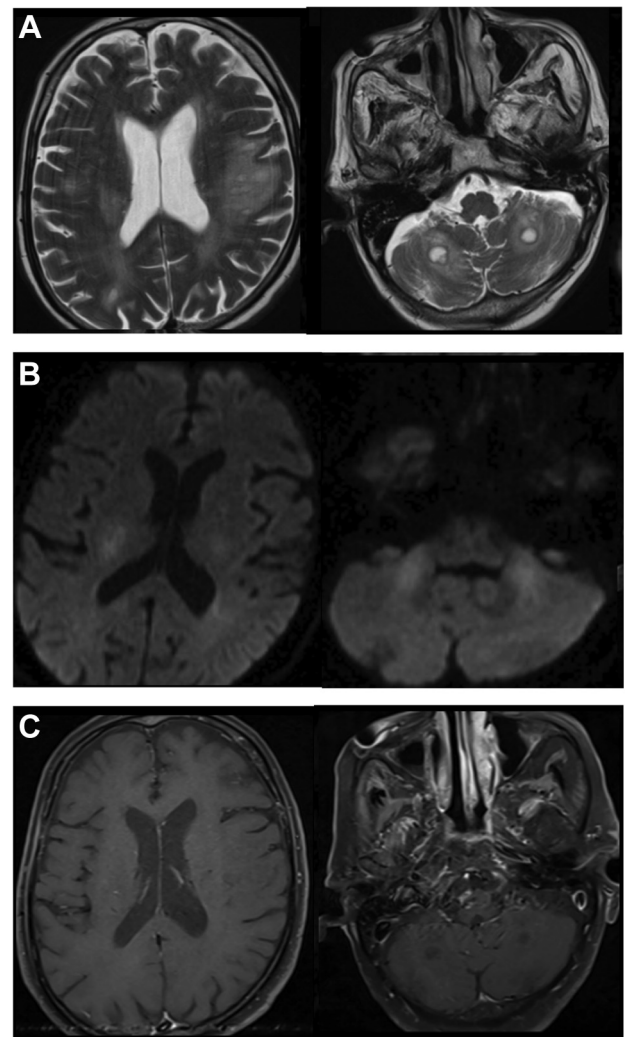


Figure 5. A 41-year-old male complaining of fever and dry cough with sudden-onset lower limb weakness, dizziness, and slurring of speech. Multifocal altered signal intensity areas, (A) T2-weighted magnetic resonance images—axial section, with no diffusion restriction, (B) diffusion weighted sequence—magnetic resonance images—axial section. No hemorrhage or postcontrast enhancement [(C) T1-weighted contrast-enhanced magnetic resonance image—axial section] in bilateral superior frontal and parietal lobes, bilateral centrum semi-ovale, corona radiata, posterior limb of internal capsules, cerebellar peduncles, and cerebellar hemispheres. In view of COVID-19 positive status, these may represent demyelinating lesions (COVID-19-associated acute disseminated encephalomyelitis).

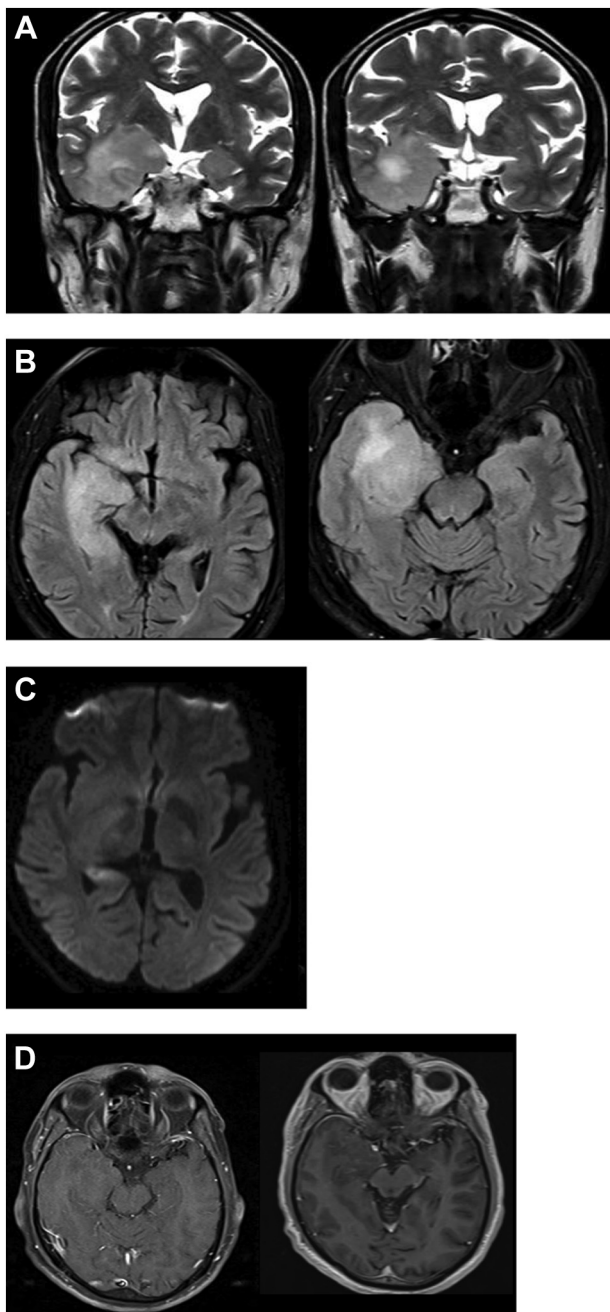


Figure 6. A 63-year-old male complaining of fever with disorientation and frontal headache; RTPCR positive. Diffuse, ill-defined, T2 and FLAIR hyperintense lesion [(A) T2-weighted magnetic resonance image—coronal section; (B) FLAIR sequence magnetic resonance image—axial section] in right anterior and medial temporal lobe involving gray as well as white matter, hippocampus and para-hippocampus, inferior portion of right gangliocapsular region without diffusion restriction [(C) diffusion-weighted sequence magnetic resonance image—axial section] or significant post-contrast enhancement [(D) T1-weighted contrast-enhanced magnetic resonance image—axial section]. Possibilities are—encephalitis—COVID encephalitis can give similar appearance.

they complained of sudden-onset lower limb weakness, dizziness, and slurring of speech. The results of the CSF bacterial and viral PCR tests were negative.

The imaging findings in this condition are multifocal, non-enhancing, altered signal intensity areas with no diffusion restriction, hemorrhage, or postcontrast enhancement involving bilateral

superior frontal and parietal lobes, bilateral centrum semiovale, corona radiata, posterior limb of internal capsules, cerebellar peduncles, and cerebellar hemispheres (Figure 5).

In exception to a few studies conducted after the onset of the pandemic, there is no clear evidence of the association between SARS-COV2 infection and demyelination (Yeh et al., 2004; Zhao et al., 2020; Parsons et al., 2020).

Encephalitis

Four patients came to our facility with disorientation for 1 day associated with frontal headache and fever for 3 days. Noncontrast head CT showed no abnormality.

MRI brain showed ill-defined, T2 hyperintense lesions in bilateral anterior and medial temporal lobes involving gray as well as white matter, hippocampus and para-hippocampus, and the inferior portion of the gangliocapsular regions without any significant postcontrast enhancement causing uncus herniation—which proved the possibility that COVID encephalitis can give a similar appearance (Figure 6).

Conclusion

In view of the broad spectrum of clinical manifestations of COVID-19 pneumonia and rapidly increasing number of cases worldwide, it has been noticed that COVID-19 is not just limited to pulmonary manifestations. Life-threatening widespread organ-specific manifestations of this infection are increasingly being appreciated. It is imperative to rapidly identify COVID-19 and its complications. Through this study, we provide an overview of neurological (extrapulmonary) manifestations caused by COVID-19, in order to hasten the diagnosis and improve management and prognosis of patients with COVID-19. In order to alert the attending physician about the neurological involvement in patients with COVID-19, it is vital that nursing staff is aware about the neurological manifestations of COVID-19 so that they can recognize changes in patients' neurological status without an undue time delay. This study highlights the need for increased CT and MR imaging in suspected patients to alert the treating physicians about the neurological complications and treat them in a timely manner as the conventional RT-PCR and serum tests are unremarkable in early onset of COVID-19. It is important to have a multidisciplinary approach and more neurology consultations in patients suspected of COVID-19 with an emphasis on prompt neuroimaging to prevent potential life-threatening complications.

CRedit authorship contribution statement

Tushar Kalekar: Conceptualization, design of the study, definition of intellectual content, and manuscript editing and reviewing. **Vaishnavi Thakker:** Literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. **Avinash Bansal:** Literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript preparation.

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