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Changes in the profile of Coronavirus disease (COVID-19) and related neuroimaging findings during the first and second waves: a South Indian perspective

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Abstract

Background The spectrum of COVID-19 infection-related neurological imaging findings in East Asian and Western populations has been well documented. In the Indian subcontinent, certain extracranial neurological imaging manifestations such as acute invasive fungal sinusitis were noted to occur with increasing frequency when compared to that reported in literature. This anomaly was more evident during the second wave of infection and since there is a paucity of literature documenting this change, we undertook this retrospective observational study.

Results Patients with COVID-19 who underwent brain or spine imaging between 1st March 2020 and 31st May 2021 were assessed for inclusion. We considered cases with imaging done in 2020 as the 1st wave, and cases with imaging done in 2021 as the 2nd wave. In the first wave, the most common neuroimaging findings were ischemic stroke (82, 26.5%), acute invasive fungal sinusitis (34, 11%), dural venous sinus thrombosis (15, 4.9%), and brain hemorrhages (15, 4.9%). In the second wave, the most common were acute invasive fungal sinusitis (44, 21.9%), ischemic stroke (39, 19.4%), and noninvasive sinusitis (30, 14.9%). The second wave had significantly more cases of acute invasive fungal sinusitis (44, 21.9% vs. 34, 11%; p-value .001), noninvasive sinusitis, and orbital cellulitis when compared to the first wave.

Conclusions While we had ischemic stroke, followed by acute invasive fungal sinusitis, dural venous sinus thrombosis, and brain hemorrhages as the most common neuroimaging findings in the first wave, the second wave was dominated by the extracranial complications of Mucormycosis, namely acute invasive fungal sinusitis.

Keywords Coronavirus disease 2019, Stroke, Acute invasive fungal sinusitis, Mucormycosis

Background

The novel coronavirus, responsible for the December 2019 outbreak of pneumonia in Wuhan, China, has spread quickly around the world leading to a global pandemic. Although the symptoms are primarily respiratory, a wide variety of neurologic manifestations have been reported, affecting up to 57.4% of patients according to an early report from Wuhan, China [1]. As the disease primarily affects the lungs causing respiratory distress and hypoxemia, there is often associated

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secondary altered mental status for which neuroimaging is obtained. According to previously published data, the most common neuroimaging findings include acute to subacute ischemic stroke, CNS inflammatory disorder, hemorrhagic stroke, cerebral microhemorrhages, and acute spontaneous intracerebral hemorrhage [2, 3]. In India, the first wave started in March 2020 with cases beginning to drop in September 2020. The second wave lasted from March to June 2021. Published data from around the world, including India, report a lower proportion of severe cases and more younger patients affected in the second wave [4–7]. There is a scarcity of data comparing the neuroimaging findings of the first and second waves of Coronavirus disease (COVID-19) in India.

It has been our practical experience that the spectrum of neuroimaging findings in India during the first wave was as described in other countries, i.e., dominated by ischemic stroke. However, during the second wave, we were seeing a predominance of invasive fungal infection and its sequelae. Being one of the largest tertiary care centers in south India, we set out to compare and contrast the COVID-19 related first and second waves demographics, clinical presentations, laboratory investigations, neuroimaging findings, and deaths.

Methods

This retrospective observational study was approved by the Institution Review Board. Consecutive patients with COVID-19 who underwent brain or spine imaging between 1st March 2020 and 31st May 2021 were assessed for inclusion. For our purposes, cases with imaging done in 2020 were considered as belonging to the 1st wave, and cases with imaging done in 2021, as the 2nd wave. From our hospital electronic data, we obtained the hospital numbers of all patients who fulfilled two criteria. First, who had a COVID-19 positive test, and second, who had neuroimaging done at any time in our hospital after that. From this cohort, we excluded patients whose neuroimaging was done >90 days (3 months) from the first COVID-19 positive result. We also excluded patients with a history of trauma, neoplasm, vascular disease, rheumatological disease, neurological disease, cardiac disease, congenital brain disorder, inherited metabolic disease, other known infection (e.g., tuberculosis), or immunological disease (e.g., multiple sclerosis). The remaining cases were included in this study for analysis.

The diagnosis of COVID-19, i.e., a COVID-19 positive status was granted based on the detection of severe acute respiratory syndrome coronavirus-2 by reverse transcription-polymerase chain reaction from nasopharyngeal swabs. From the patient’s clinical notes, we noted that neuroimaging was done either due to a primary presentation with neurological symptoms or due

to the development of neurological signs or symptoms during the hospital admission period. The mean duration between a positive COVID-19 test result and neuroimaging was 3 days (range of 0–85 days).

CT imaging was performed using 128-slice multi-detector CT systems (Philips Incisive CT, Koninklijke Philips N.V, Netherlands, and GE Discovery 750 HD, GE Healthcare, Illinois, United States). MRI was performed using either a 1.5 T Siemens Avanto Dot system with a 10-channel phased array head and neck coil or a 3 T Siemens Magnetom Skyra system with 32-channel phased array head coil (Siemens, Erlangen, Germany). Demographic information (Table 1), risk factors like diabetes, hypertension, kidney and cardiac disease, initial presenting symptoms, laboratory parameters, duration of admission, and neuroimaging findings were recorded. Images were reviewed by two consultant radiologists who were blinded to each other. In case of a discrepancy, the opinion of a third was sought which was considered final. The list of imaging findings is enumerated in Table 2. Continuous variables were presented as mean and standard deviation and student’s t-tests were used to compare two groups. Categorical variables were presented as frequencies and proportions with groups compared using Fisher’s exact test. Statistical significance was set at $p < 0.05$.

Results

Between 1st March 2020 and 31st May 2021, 1532 patients who presented to our hospital were both positive for COVID-19, and also had neuroimaging done. Of these, 1020 patients were excluded. Of the remaining 512 patients, 309 (60.4%) presented in the 1st wave, and 203 (39.6%) in the 2nd wave.

Table 1 Sex and age distribution between the two waves

	1st wave		2nd wave		p-value
	Total	% within wave	Total	% within wave	
Sex					
Male	217	70.2	125	61.6	0.04
Female	92	29.8	78	38.4	
Age					
< 20	7	2.3	16	7.9	0.02
21–30	21	6.8	12	5.9	
31–40	45	14.6	37	18.2	
41–50	71	23	29	14.3	
51–60	64	20.7	43	21.2	
61–70	58	18.8	33	16.3	
71–80	37	12	25	12.3	
> 80	6	1.9	8	3.9	
Total	309	100	203	100	

Table 2 Neuroimaging findings between the two waves. Relevant data from Chowdhary et al., and Choi et al. is also tabulated for comparison (MCA—middle cerebral artery; ICA—internal carotid artery; AIFS—acute invasive fungal sinusitis; ICP—intracranial pressure; PRES—posterior reversible encephalopathy syndrome; AHNE—acute hemorrhagic necrotizing encephalitis; CLOCC—cytotoxic lesion of the corpus callosum)

Imaging findings	1st wave		2nd wave		Total		p-value	Chowdhary et al. (%)	Choi et al. (%)
	n	%	n	%	n	%			
Dural sinus thrombosis	15	4.9	2	1	17	3.3	0.02		
Cavernous sinus thrombosis	5	1.6	7	3.5	12	2.4	0.23		
MCA thrombosis	3	1	2	1	5	1	1.00		
ICA thrombosis	8	2.6	4	2	12	2.4	0.77		
Vertebral artery thrombosis	2	0.7	0	0	2	0.4	0.52		
AIFS	34	11	44	21.9	78	15.3	0.001		
Noninvasive sinusitis	9	2.9	30	14.9	39	7.6	<0.001		
Orbital cellulitis	1	0.3	29	14.4	30	5.9	<0.001		
Otomastoiditis	4	1.3	3	1.5	7	1.4	0.62		
Brain abscess	4	1.3	4	2	8	1.6	1.00		
Skull-base osteomyelitis	5	1.6	2	1	7	1.4	0.53		
Raised ICP	12	3.9	4	2	16	3.1	0.45		
Cerebral edema	1	0.3	2	1	3	0.6	0.63		
Ischemic stroke	82	26.5	39	19.4	121	23.7	0.06	36.2	24
Hemorrhagic stroke	4	1.3	2	1	6	1.2	0.74	24	
Encephalitis	4	1.3	3	1.5	7	1.4	0.81	14	3.3
Meningitis	6	1.9	4	2	10	2	0.54		
PRES	3	1	4	2	7	1.4	0.78	25.7	
Demyelination	2	0.6	2	1	4	0.8	0.64		
Transverse myelitis	1	0.3	2	1	3	0.6	0.63		
AHNE	1	0.3	0	0	1	0.2	0.60		
CLOCC	1	0.3	0	0	1	0.2	0.60		
Macrohemorrhages	15	4.9	1	0.5	16	3.1	0.007		5.4
Microhemorrhage	3	1	0	0	3	0.6	0.42		6.9
Non-specific T2 hyperintensity	9	2.9	0	0	9	1.8	0.01		
White matter hypodensity	7	2.3	0	0	7	1.4	0.01		

Demographic and baseline characteristics

The mean age of patients in the 1st wave was 52 years and, in the 2nd, was 50 years. In both waves, the largest age cohort was the 51–60 year age group (20.7% vs 21.2%). There was a significantly higher number of under 20-year-olds (7, 2.3% vs.16, 7.9%; p-value 0.02), and a lower number of over 60-year-olds affected in the 2nd wave (58, 18.8% vs.33, 16.3%; p-value 0.02). In both waves, males outnumbered females with a significantly higher percentage in the first wave (217, 70.2% vs.125, 61.6%; p-value 0.04).

Clinical profile and laboratory analysis

A significantly higher number of patients presented with neurological symptoms in the first wave (215, 69.8% vs.114, 56.4%; p-value 0.002). The remaining patients did not present with neurological symptoms but developed them during the course of admission.

The most common neurological presenting symptoms in the first wave were headache (21.1%), stroke (18.8%), and altered sensorium (17.5%). In the second wave, the most common were altered sensorium (16.5%), headache (15.6%), and stroke (14.9%). There were significantly more clinical presentations of stroke (0.002), and myalgia (0.008) in the first wave. There was no significant correlation between presenting neurological complaints and abnormal findings on imaging.

The most common general symptoms were fever (30.2%), dyspnea (17.3%), cough (15.6%) in the first wave, and fever (36.6%), cough (19.8%), and dyspnea (18.3%) in the second wave. The most common comorbidity in both the first and second waves was diabetes (42.9% vs 33.1%), followed by hypertension (45.6% vs 28.7%). There was no significant difference in general symptoms and comorbidities between the waves.

Patients in both waves showed elevated levels of random blood glucose (98.4% vs 94.6%), d-dimer (87.7% vs 94.1%), and lactate dehydrogenase (91.6% vs 95.1%), with no significant differences between them.

Neuroimaging characteristics

Nearly an equal percentage of cases had abnormal neuroimaging in the first and second waves respectively (189, 61.2% vs 127, 62.6%). In the first wave, the most common neuroimaging findings were ischemic stroke (82, 26.5%), acute invasive fungal sinusitis (AIFS) (34, 11%), dural venous sinus thrombosis (15, 4.9%), and brain hemorrhages (15, 4.9%). In the second wave, the most common neuroimaging findings were AIFS (44, 21.9%), ischemic stroke (39, 19.4%), and noninvasive sinusitis (30, 14.9%). There were significantly more cases of dural sinus thrombosis (15, 4.9% vs. 2, 1%; p -value 0.002), and hemorrhages (15, 4.9% vs. 1, 0.5%; p -value 0.007) in the first wave with respect to the second wave. The second wave had significantly more cases of AIFS (34, 11% vs 44, 21.9%; p -value 0.001), noninvasive sinusitis (9, 2.9% vs. 30, 14.9%; p -value <0.001), and orbital cellulitis (1, 0.3% vs. 29, 14.4%; p -value <0.001) when compared to the first wave. Acute hemorrhagic necrotizing encephalitis (1, 0.3%), cytotoxic lesion of the corpus callosum (1, 0.3%), vertebral artery thrombosis (2, 0.7%), microbleeds (3, 1%), non-specific T2 hyperintensities (9, 2.9%), and white matter hypodensities (7, 2.3%) were only seen during the first wave (Table 2).

Surgery and mortality

There were significantly more surgeries in the second wave (33, 10.7% vs 42, 20.8%; p -value 0.002). The most common surgeries in both waves were functional endoscopic sinus surgery (28, 9.1% vs 41, 20.2%) followed by decompressive craniectomy (2, 0.6% vs 1, 0.5%). There were 49 deaths during the first wave, in 15.9% of the cohort. Of these, 18 were in patients with ischemic stroke (36.7%), 4 in patients with hemorrhage (8.2%), and 2 in patients with AIFS (4%). There were 40 deaths during the second wave, in 19.8% of the cohort. The most common causes were ischemic stroke (15, 37.5%), and AIFS (11, 27.5%). There was no significant correlation between the presence of abnormal imaging and death. Further comparison data is available in the Additional file 1.

Discussion

A database search and systematic review of case reports and case series from 1 December 2019 to 30 September 2020 by Chowdhary et al. found 171 COVID-19 patients from 134 studies with neurological complications. The mean age of patients was 53.2 years, with males (66.7%) outnumbering females (33.7%). The most common

neuroimaging findings were ischemic stroke (62, 36.2%), followed by CNS inflammatory disorder (44, 25.7%), and hemorrhagic stroke (41, 24.0%) [2]. Another database search, systematic review, and meta-analysis by Choi and Lee reviewed articles published between January 1, 2020, and October 9, 2020. They found 21 eligible articles with 2125 patients. The most common neuroimaging findings were acute to subacute infarcts (24%), cerebral microhemorrhages (6.9%), acute spontaneous intracerebral hemorrhages (5.4%), and encephalitis/encephalopathy (3.3%) [3].

In our study, nearly 2 out of 3 patients in both waves had some abnormal neuroimaging. Like the meta-analyses cited above, the most common neuroimaging finding in the first wave was acute to subacute ischemic stroke (Fig. 1). We had 82 cases of this with an incidence of 26.5%, similar to the data of Choi and Lee (24%) [3]. A multicenter retrospective study of all COVID-19-related stroke patients from 13 hospitals in south India over 3 months (June–August 2020) had ischemic stroke as the most predominant stroke subtype (97% of patients). Similar to our study (70.2% males, mean age of 52 years, 42.9% diabetic, 45.6% hypertensive), they had a male predominance, mean age of 55 years, and diabetes/hypertension as the predominant comorbidities. Furthermore, in 16/62 (26%) of cases, their patients did not have any conventional risk factor for stroke [8]. In the second wave, we had 39 cases of acute to subacute ischemic stroke, with an incidence of 19.4%. This reduced incidence in the second wave, although insignificant (0.06), was likely due to the early use of heparin, better hydration, lower number of older patients (>60 years) affected, and increased public awareness. In both waves combined, we had 121 cases of ischemic stroke, of which 26.4% of patients had no prior risk factors.

The second wave of COVID-19 in India was a staggering healthcare crisis with an unlikely villain—Mucormycosis. While its increased incidence in the second wave in India has been documented [9, 10], our PubMed and Google Scholar database search revealed no articles comparing the neuroimaging findings of the two waves of COVID-19 in India. This fungus of the *Mucorales* order is ubiquitous in the environment and causes opportunistic infections in humans. Even though the estimated pre-COVID prevalence of this infection in India was higher than in developed countries [11], the staggering increase in cases especially during the second wave of COVID-19 was unprecedented. Many factors were suspected to play a hand in this “syndemic”, such as the high prevalence of diabetes in India, overdose and indiscriminate use of systemic steroids by the medical fraternity and lay-people alike, possible immune effects of the newer variants of COVID-19, prolonged ICU stay, and the presence of

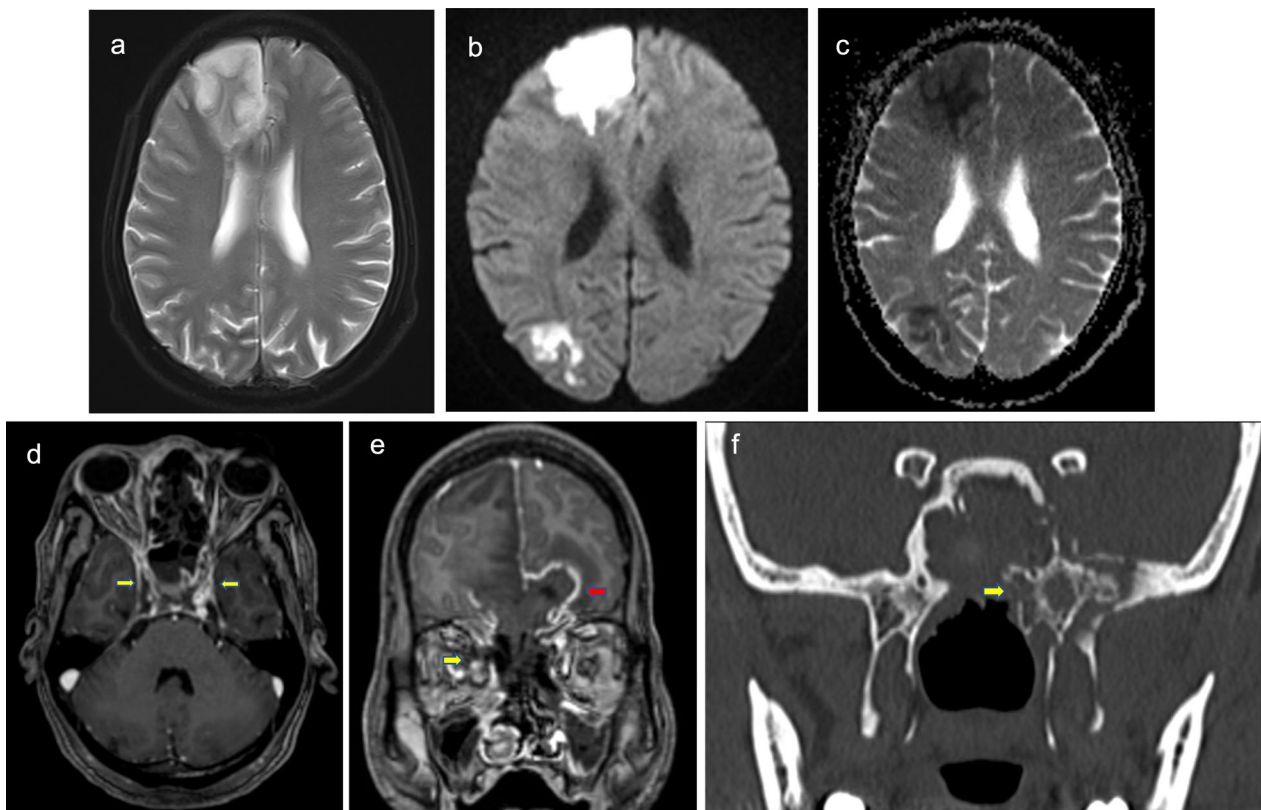


Fig. 1 This 52-year-old gentleman with uncontrolled diabetes and COVID-19 presented with insidious-onset, progressively worsening bifrontal and retro-orbital headache with loss of vision in both eyes. MRI revealed features of ischemic stroke in the right ACA and posterior watershed territories (a-T2W, b-DWI, c-ADC), complete non-enhancement in right and partial non-enhancement of left cavernous sinus suggestive of thrombosis (d-T1W axial post-contrast, yellow arrows), and non-enhancing mucosa lining the nasal cavity and maxillary sinuses, extension of disease into the orbits (yellow arrow, right orbit) with a bifrontal abscess (red arrow) (e-T1W coronal post-contrast) suggestive of aggressive invasive infection. CT revealed extension of disease from the sphenoid sinus with permeative destruction of the left sphenoid bone (yellow arrow) (f-coronal CT). Surgical exploration and histopathological correlation revealed rhinocerebral Mucormycosis with brain abscess

other comorbidities [12, 13]. The effects of this Mucormycosis 'syndemic' were acutely felt during the second wave in India more than in any other country. According to a systematic review by Pal et al., 72% of all cases were reported from India [14]. The most common form of Mucormycosis is the rhino-orbito-cerebral type, referred to as AIFS in this article. The infection typically begins in the nasal cavity in the region of the middle turbinate, then quickly spreads into the sinuses, orbits, and brain without respect for anatomical boundaries due to its invasive nature. The diseased tissue is prone to necrosis, and the development of black eschars in the nasal cavity. On MRI it appears as contiguous foci of non-enhancing tissue, the so-called black turbinate sign, which can aid in early imaging diagnosis (Fig. 2). There are often associated cranial nerve deficiencies, vascular thromboses, and infarctions [15, 16]. In our study, there were only 34 cases of AIFS in the first wave (11%), which increased significantly to 44 cases (21.9%) in the second wave (p-value 0.001). We considered any extension of disease on CT/

MRI to the peri-antral fat, pterygopalatine fossa, sphenopalatine foramen, orbits, vessels, bone, cavernous sinus, or brain as AIFS [17]. Most of these cases of AIFS diagnosed on imaging went on to have surgical confirmation with functional endoscopic sinus surgery (28 in 1st wave, and 41 in the 2nd wave), while the remainder were conservatively managed. On the other hand, mucosal thickening and sinus opacification without bone erosion or extra-sinus extension were considered as noninvasive sinusitis. Interestingly, there were only 9 cases of non-invasive sinusitis in the first wave (2.9%), which significantly increased to 30 cases (14.9%) in the second wave (<0.001). Although there were no explicit imaging features of invasion in these cases, the significant increase in the second wave suggests that at least some of these cases represent an early / pre-invasive form of AIFS.

Therakathu et al. had shown that the most common site of extra-sinus involvement in Rhinocerebral Mucormycosis is the orbit [18]. We found a significant increase in cases of orbital cellulitis in the second wave (1, 0.3% vs 29,

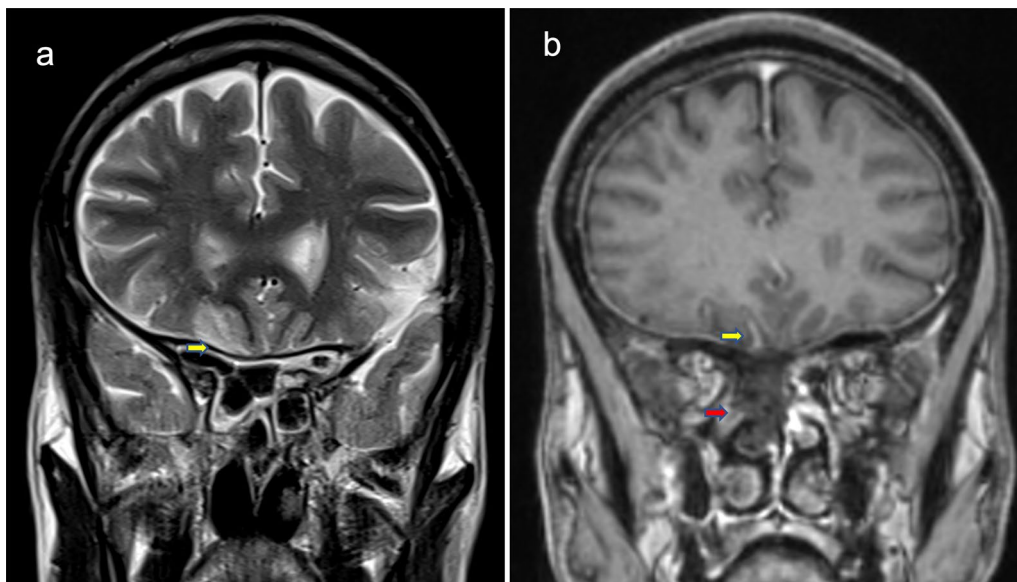


Fig. 2 This 58-year-old gentleman, a known diabetic and hypertensive, and RT-PCR COVID-19 positive presented with bitemporal headache. MRI revealed gyral swelling and hyperintensity in the right inferior frontal lobe (a-T2W coronal, yellow arrow), with thickening and enhancement of the overlying sulcal leptomeninges suggestive of meningoencephalitis (yellow arrow) (b-T1W coronal post-contrast). There is also lack of enhancement of the right middle turbinate, and ethmoid air cells suggestive of the black turbinate sign (red arrow), pointing to invasive fungal rhinosinusitis as the cause of the intracranial pathology

14.4%; p -value < 0.001) consistent with this data. Other non-fungal infective/inflammatory conditions such as otomastoiditis, brain abscess, and skull-base osteomyelitis had no difference in incidence between the waves.

The relationship between large and small-vessel cerebrovascular thrombosis, and COVID-19 is well-established. The causes of thrombosis include virus-induced endothelial damage, cytokine storm, and elevated procoagulant markers [19, 20]. Cheruiyot et al. in a systematic review found the incidence of arterial thrombosis in critically ill admitted patients to be 4.4% [21]. We found 13 cases of MCA, ICA, and vertebral artery thrombosis in the first wave (4.3%), and 6 cases in the second wave (3%). Dural sinus thrombosis was significantly more in the first wave (15, 4.9% vs 2, 1%; p -value 0.02), its position having been usurped by rhinocerebral fungal infections and its attendant complications in the second wave. The reasons mentioned earlier for the reduced incidence of stroke in the second wave could be the cause of the reduced incidence of thrombosis as well. Cavernous sinus thrombosis which has been linked to fungal infection [22] showed no difference between the waves.

Macrohemorrhages including intracranial, subarachnoid, and subdural hemorrhages were seen in 15 (4.9%) cases in the first wave, significantly dropping to just 1 (0.5%) case in the second wave (0.007). While our first wave data are similar to that of Choi and Lee (5.4%),

the low number of cases in the second wave is likely due to the preponderance of fungal sinusitis and its complications.

We found no significant difference in the incidence of cerebral edema, raised intracranial pressure, hemorrhagic stroke, encephalitis, meningitis, posterior reversible encephalopathy syndrome, demyelination, and transverse myelitis between the two waves. We suspect that the presence of acute hemorrhagic necrotizing encephalitis (Fig. 3), and cytotoxic lesion of the corpus callosum only during the first wave is likely due to the relative rarity of these conditions. Further, non-specific T2 hyperintensities and white matter hypodensities that were only seen during the first wave are likely incidental or due to leukoencephalopathy.

Limitations

Our study has a few limitations. Firstly, it was a retrospective observational single-center study that limits its external validity. Secondly, the attribution of the neuroimaging findings to COVID-19 is limited by the lack of a control group. Thirdly, we did not consider the chronic and long-term findings as we only included cases with a ≤ 3 -month interval between COVID-19 positivity and brain imaging.

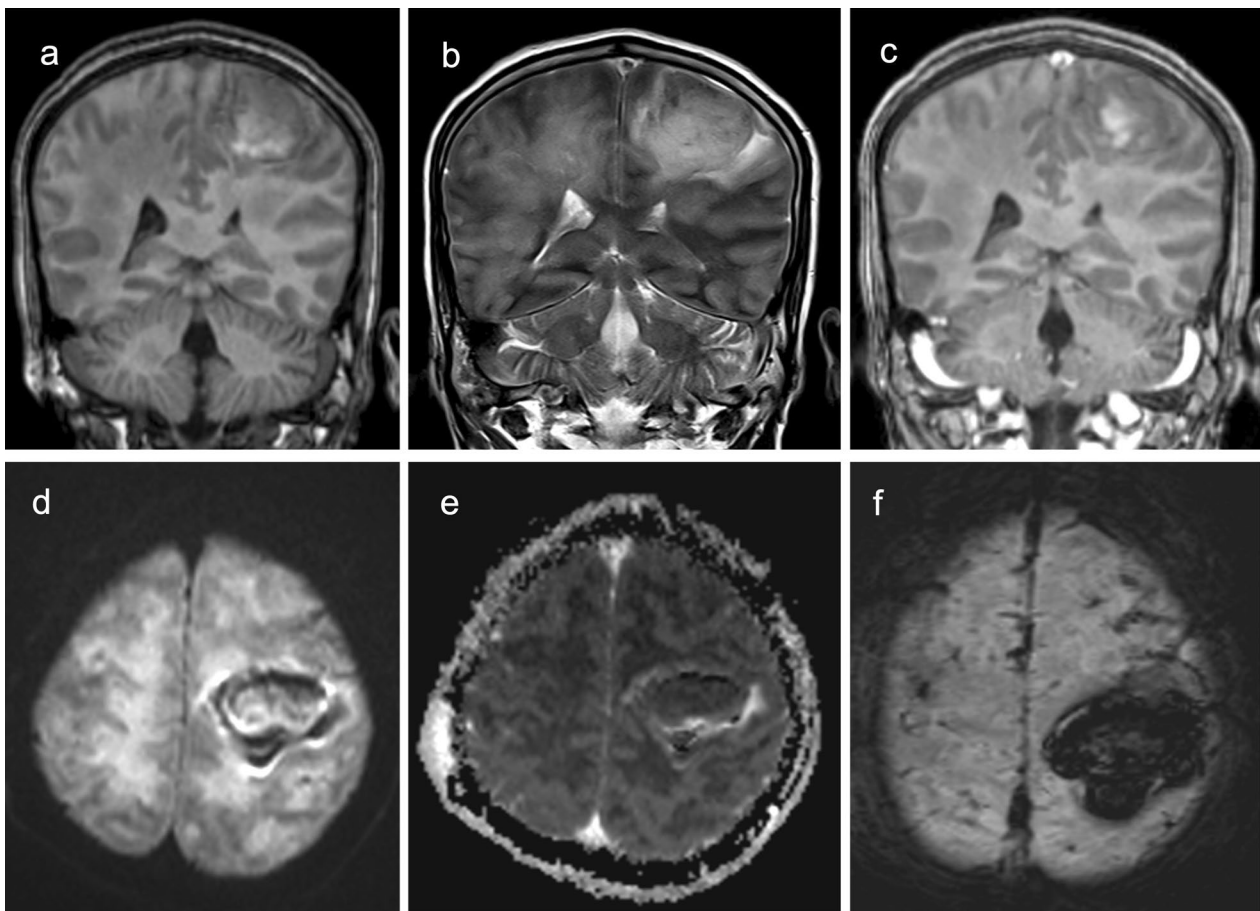


Fig. 3 This 39-year-old gentleman, a known diabetic and alcoholic presented with altered sensorium. He was COVID-19 positive at presentation. MRI reveals diffuse cerebral edema with effacement of cerebral sulci, cytotoxic edema in bilateral cerebral deep white matter (a-T1 coronal, b-T2 coronal, c-T1 coronal post-contrast) with multiple foci of white matter predominant hemorrhage involving bilateral cerebral hemispheres, and a large hematoma is in the left frontoparietal region (d-DWI, e-ADC, f-SWI)

Conclusions

As this current pandemic continues to evolve and the virus makes its way through different demographics and socio-economic groups, a different picture is emerging in the developing world. Our study, done in one of the largest tertiary care hospitals in South India, highlights this change. While we had Ischemic stroke, followed by AIFS, dural venous sinus thrombosis, and brain hemorrhages as the most common neuroimaging findings in the first wave, the second wave was dominated by the extracranial complications of Mucormycosis, namely AIFS. Furthermore, the related findings of noninvasive sinusitis, and orbital cellulitis had significantly increased in the second wave. While the peak age cohorts were unchanged, there were a greater number of younger patients involved in the second wave. This study serves to track the change in the spectrum of neuroimaging findings of COVID-19 in the developing

world, hopefully informing the medical fraternity of the same, and in the process guiding future research.

Abbreviations

COVID-19 Coronavirus disease 2019
AIFS Acute invasive fungal sinusitis

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s43055-023-01125-7>.

Additional file 1. Further details on the exclusion data, and comparison between the waves is provided in this file.

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Author contributions

MM contributed to conceptualization, methodology, software, formal analysis, investigation, data curation, writing—original draft, review and editing, project administration. AJ contributed to conceptualization, methodology, validation,

writing—review and editing, supervision. PM contributed to conceptualization, methodology, validation, writing—review and editing, supervision, project administration. SA contributed to writing—review and editing, supervision. AS contributed to writing—review and editing, supervision. ATP contributed to writing—review and editing, supervision. HV contributed to writing—review and editing. BTS contributed to writing—review and editing statement—all authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval was granted by the Institute ethics board, the need for consent was waived as only anonymized patient images and data were used.

Consent for publication

Deemed unnecessary by the Institute ethics board as only anonymized patient images and data was used. The authors declare that no identifiable patient data/images are used.

Competing interests

The authors declare that they have no competing interests.

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