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MRI findings in COVID-19 positive and COVID-19 negative patients presenting with acute neurological symptoms – a case-control study

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Abstract

Background & Objective: Neurological manifestations of novel-coronavirus disease (COVID-19) have been described in various studies. None of these studies has compared the findings in COVID-19 patients with COVID-negative patients presenting with similar clinical symptomatology during the same period. We undertook this case-control study with an aim to establish a direct relationship between COVID-19 infection and CNS related clinical and imaging presentations. *Methods:* This study was a review of retrospectively collected data of the patients who presented with different neurological symptoms to a tertiary care hospital in India. Based on results of Reverse transcriptase-polymerase chain reaction for SARS-Co-V-2, patients were classified into COVID-19 positive and COVID-19 negative groups. MRI findings in both groups were reviewed for acute ischemic stroke, intracranial bleed and other acute imaging abnormalities. Basic demographic information and stroke-related co-morbidities were also compared. Results: Eighty four patients in COVID-19 positive group and 323 patients in COVID-19 negative group underwent brain MRI for acute neurological symptoms during the same period. There was no statistically significant difference in presenting symptoms, sex distribution and risk factors for stroke. There was a higher prevalence of increased coagulability in COVID-19 positive group (p-value = 0.009). No statistically significant association was observed for infarcts or their hemorrhagic transformation, intracranial bleed, intracranial infection or dural sinus thrombosis. An association was found between acute diffuse leukoencephalopathy and COVID-19 infection (p value < 0.05).
Conclusion: The current study points towards a weak direct association between COVID-19 infection and acute abnormalities in MRI brain studies, especially in patients with pre-existing co-morbidities.

Keywords: COVID-19, MR imaging, Stroke, Brain hemorrhage, Leukoencephalopathy

INTRODUCTION

The novel-coronavirus disease (COVID-19) pandemic is an evolving situation and has probably been the most researched condition in modern times. Multi-organ system involvement has been described in the literature with many studies have focused on neurological manifestations of the viral illness.[1-8] Direct CNS invasion, cytokine storm, coagulopathies and autoimmunity have been proposed as possible pathogenesis in CNS involvement.[9,10] Hematological and olfactory route of CNS spread have been suggested with neuronal invasion by angiotensin-converting enzyme 2 receptors. Coagulation abnormalities and cytokine storm have been proposed as risk factors for stroke.[9,10]

Few studies have described neurological manifestations on imaging with similar findings with wide variation in frequency.[8,11-13] None of these studies has compared the findings in COVID-19 positive with COVID-negative patients presenting with similar clinical symptomatology during the covid pandemic period. We undertook this case-control study with an aim to establish a direct relationship between COVID-19 infection and CNS complications. We compared the MRI findings between patients presenting with acute neurological symptoms in COVID-19 positive group with COVID-19 negative group during the same period. To the best of our knowledge, no previous study has compared the acute MRI

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abnormalities in COVID-19 infection as a case-control study presenting with acute neurological manifestations.

METHODS

This study was a review of retrospectively collected clinical, laboratory and imaging data from the Departments of Radiology and Neurology of a tertiary care hospital in North India.

Medical records of all patients who underwent MRI Brain study from March 2020 to December 2020 for different neurological symptoms were reviewed. Based on results (sampled at the time of admission) of reverse transcriptase polymerase chain reaction test for SARS-CoV-2 virus (RT-PCR for SARS-Co-V-2), patients were classified into COVID-19 positive and COVID-19 negative groups.

Clinical and MRI findings for all patients in both groups were reviewed for acute ischemic stroke, intracranial hemorrhage or other acute imaging abnormalities those may explain neurological emergencies. Patients with chronic imaging findings were classified separately.

The inclusion criteria were: 1. Patients presenting to the Emergency Department with acute neurological symptoms and had undergone brain MRI; 2. Patients admitted in the hospital and had undergone brain MRI for evaluation of acute neurological symptoms. The exclusion criteria were: 1. Patients under the age of 18 years; 2. Patients with intracranial neoplasms or those in follow-up for known intracranial disease; 3. Patients with studies showing motion artifact precluding diagnostic interpretation.

Basic demographic information, co-morbidities (cardiac disease, diabetes mellitus, hypertension, chronic kidney disease and altered coagulation profile) and course in the hospital was accessed from hospital records for all patients. Diagnosis of cardiac disease as a cause of stroke was based on echocardiography diagnosis of atrial thrombus, cardiac tumors or valvular disease.[14] Chronic kidney disease was defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause.[15] Coagulopathy was defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s.[16] Diabetes mellitus was diagnosed using A1C test, with a threshold of ≥6.5%.[17] Presenting acute neurological symptoms were recorded for all patients.

MRI technique

Imaging was performed at 3.0T MRI (Philips Health Systems, the Netherlands) with a 15-channel head coil. Imaging was planned according to the neurological manifestations. In suspected patients for stroke, a quick protocol consisting of axial diffusion weighted imaging (DWI), susceptibility weighted imaging (SWI), axial fluid attenuating inversion recovery (FLAIR), and arterial spin labeling ASL perfusion imaging were performed followed by 3D time of flight MR angiography (3D TOF MRA) of brain vessels. If no ischemia was detected by the attending radiologist, a 3D FLAIR sequence was added. In patients with other neurological manifestations, axial DWI, SWI, 3-dimensional FLAIR, axial T1W and axial T2W were performed. MR venography (2D TOF) and post contrast T1 imaging were done if asked by a neurologist or at the discretion of attending radiologist on case-by-case basis. For 2D T2-W-TSE, the imaging parameters used were repetition time (TR)/echo time (TE) 3422 ms/108 ms, slice thickness 5 mm, flip angle 90°, acquisition matrix = 384 × 384, and field of view (FOV) = 230 × 230 mm^2. The imaging sequence for post-contrast 3D T1-W TSE sequence was TR/TE of 700 ms/26 ms, slice thickness 0.9 mm, FA = 90°, acquisition matrix = 224 × 278 and FOV= 200 × 250mm2. SWI with phase imaging was used to differentiate calcification from chronic hemorrhage. Calcification, as well as chronic hemorrhage, appeared as hypointense on magnitude images. On the filtered phase images, blood products showed a negative phase, and calcifications showed a positive phase. The imaging parameters used for SWI were four echoes at 5.6, 11.8, 18, and 24.2 ms with (TR) = 31 m; FA = 17, slice thickness = 1 mm, acquisition matrix = 384 × 384, FOV = 240 × 240 mm^2.

Image interpretation

MRI Brain studies for all patients in both groups were studied by two radiologists on Philips work station (with over 35 years and 9 years' experience) and their findings were recorded independently. All disagreements were resolved after mutual discussion. All acute infarcts /acute ischemia were recorded and classified into large vessel, small vessel and embolic infarcts. Large vessel infarcts were defined as cerebral, brainstem or cerebellar infarcts with extracranial or intracranial thrombus / dissection. Small vessel infarcts were defined as deep (< 1.5 cm) infarcts in brainstem, thalamus or basal ganglia without obvious large

vessel occlusion. Embolic infarcts were classified if there were scattered infarcts in multiple vascular territories. All intracranial bleeds were recorded with its age (acute, subacute or chronic) and location (intraparenchymal, extra-axial or subarachnoid). Microhemorrhages, defined as multifocal small areas of susceptibility on SWI with negative phase without signal abnormality on T1W/FLAIR images, were presumed as chronic finding and were not interpreted as COVID-19 related findings.

Discreet or confluent T2/FLAIR hyperintensities in the subcortical white matter not showing diffusion restriction were presumed as microvascular chronic ischemia, also interpreted as chronic findings. Acute diffuse white matter encephalopathy was defined as diffuse restricted diffusion in the white matter, not conforming to either ICA territory. Intracranial venous system was routinely assessed for every patient on SWI and FLAIR images with venography in selected patients as decided by the attending radiologist supervising the study.

The age / sex distribution, presenting symptoms, co-morbidities, acute MRI abnormalities and mortality were analyzed in COVID-19 positive and negative groups.

Statistical analysis

The variables between COVID-19 positive and COVID-19 negative group were compared using Z-test. A p value of ≤ 0.05 was considered to indicate a statistically significant difference among all the variables. All statistical analysis was performed with SPSS version 18 statistical software for Windows (SPSS; SPSS Inc.; Chicago, IL, USA)

RESULTS

During the course of the study, a total of 3,021 RT-PCR diagnosed COVID-19 positive patients received treatment at the hospital. Eighty four (COVID-19 positive group) underwent Brain MRI for evaluation of acute neurological symptoms. In the COVID-19 negative group, 329 patients underwent Brain MRI for evaluation of acute neurological symptoms during the same period. Six patients who had intracranial neoplasms were excluded in the COVID-19 negative subgroup (N=323). Twelve (12/84) patients in COVID-19 positive group and 32/323 patients in COVID-19 negative group underwent contrast imaging. Nine (9/84) patients and 21/323 patients were evaluated with MR venography in COVID-19 positive and negative groups respectively. No patients were excluded for suboptimal imaging from either group.

Demographics: In the COVID-19 positive group (N=84), there were 63 males and 21 females which were statistically comparable to the COVID-19 negative group (N=323, 228 males and 95 females) with *p value* = 0.4. Mean age in both subgroups was also comparable (66.3 years in COVID-19 positive group and 66.2 years in COVID-19 negative group).

Presenting chief symptom: Stroke like symptoms were the most common neurological presentation in both the groups (41/84 and 181/323) followed by altered mental status (17/84 and 43/323) and headache (12/84 and 57/323). Unconsciousness, seizure, vertigo and fall were other presenting symptoms. There was no statistically significant difference in presenting symptoms in both the groups (*p values* varying between *0.112 to 0.726*).

Major stroke risk factors: Five (5/84) patients in COVID-19 positive group had chronic kidney disease as compared to 25/323 patients in the COVID-19 negative group (*Z value= -0.559, p value = 0.6*). Echocardiography was done for all patients in both subgroups as a part of work-up. In the COVID-19 positive group, 3/84 patients were diagnosed with atrial thrombus and 1/84 patients were diagnosed with atrial myxoma and mitral valvular disease each. In the COVID-19 negative group, 5/323 patients had atrial thrombus and valvular heart disease while 4/323 patients had atrial myxoma. There was no statistically significant difference in prevalence of cardiac disease between both groups (*Z value = 0.967, p value =0.332*). Prevalence of diabetes mellitus and hypertension was also comparable in both groups (19/84 vs 64/323, *Z value= 0.568, p value = 0.6* for diabetes mellitus and 34/84 vs 142/323, *Z value - -0.5746, p value = 0.567* for hypertension). Patients in COVID-19 positive group had a higher prevalence of altered coagulation profile at initial assessment as compared to those in the COVID-19 negative group (9/84 vs 21/323; *Z-value = 0.26, p-value = 0.009*).

Patient demographics and clinical details are summarized in Table 1.

MRI findings

Acute infarction: Acute infarction was the most common MRI finding reported in both groups

Table 1: Summary of patient demographics and clinical details with result of the Z-test for two population proportions analysis between two groups

S.No	Parameter	Measures			
		COVID-19 positive	COVID-19 negative	z-value	p-value
1.	Total number	N=84	N=323		
2.	Mean age (years)	63.3	66.2		
3.	Sex distribution (M: F)	63:21	228:95	0.79	0.42
4.	Chief symptom				
	Stroke like symptoms	41/84	181/323	-1.185	0.234
	Altered mental status	17/84	43/323.	1.1595	0.112
	Headache	12/84	57/323	-0.731	0.465
	Unconsciousness	7/84	23/323	0.379	0.704
	Seizures-like episodes	3/84	4/323	1.465	0.142
	Vertigo	2/84	10/323	-0.345	0.726
	Fall	2/84	5/323	0.523	0.603
5.	Chronic kidney disease	5/84	25/323	-0.559	0.575
6.	Cardiac disease	5/65	13/276	0.967	0.332
7.	Diabetes Mellitus	19/84	64/323	0.568	0.569
8.	Hypertension	34/84	142/323	-0.5746	0.567
9.	Altered coagulation profile	9/84	21/323	**0.258**	**0.009**

*p value ≤ 0.05 is considered significant

(15/84, 17.9% and 34/323, 10.5%). Although the incidence of acute infarction was higher in COVID-19 positive group, they did not differ statistically (*Z value=1.84, p value: 0.065*). Out of 15 patients in the COVID-19 positive group 4 (26.7%) had large vessel infarction while 7(46.7%) had small vessel infarction. 4/15 (26.7%) patients in the COVID-19 positive group showed embolic infarcts. In the COVID-19 negative group, the incidence of large vessel, small vessel and embolic infarctions was 9/34 (26.4%), 18/34 (52.9%) and 7/34 (20.5%) respectively. No statistically significant difference was found in any of these subgroups between COVID-19 positive and COVID-19 negative patients (*p values 0.638 to 0.992*). Among the small vessel infarcts, hemorrhagic transformation and multifocality was compared between both groups without any statistically significant difference (*p values 0.285 and 0.502*). Similar results were observed in hemorrhagic transformation of large vessel infarcts (*p value = 0.522*).

Intracranial bleed: Four (4/84, 4.7%) patients in COVID-19 positive group had evidence of acute onset intracranial bleed on MRI, out of which 3 (75%) were intraparenchymal and 1/4 (25%) had acute subdural hematoma. In the COVID-19 negative group, 14/323 (4.3%) patients had acute intracranial bleed, out of which 10 (71.4%) were intraparenchymal and 2 (14.3%) each were subarachnoid and subdural in location. No subarachnoid hemorrhages were seen in the COVID-19 positive group. The incidence of bleed or distribution in any subgroup did not differ statistically (*p values 0.424 to 0.889*).

Acute diffuse white matter encephalopathy: Two (2/84, 2.4 %) patients in COVID-19 positive group presented with rapidly deteriorating consciousness during admission in the hospital. MRI revealed acute diffuse white matter encephalopathy. Similar MRI findings were seen in one patient in the COVID-19 negative group (1/323, 0.3%) who was admitted in cardiac intensive care for left ventricular dysfunction. This difference was statistically significant with *Z-value = 1.977 and p value = 0.047*.

Infection: Two (2/84, 2.4%) patients in the COVID-19 positive group had findings of acute infection on MRI. One of these patients had paranasal sinus infection with intracranial extension in form of extradural abscess. Other patient had diffuse pachy-meningeal enhancement with orbital inflammation. Eight (8/323, 2.5%) patients in the COVID-19 negative group showed intracranial infections. 5/8 patients had

leptomeningeal enhancement; 3 patients had intra-parenchymal abscess. Overall, the difference in intracranial infection in the two groups was statistically insignificant with *Z-value = -0.050* and *p value = 0.960*.

Dural sinus thrombosis: Only 1/84 (1.1%) patients in COVID-19 group presented with dural sinus thrombosis. This patient was a 45-year-old female with chronic myeloid leukemia. In the COVID-19 negative group 2/323 (0.6%) patients had dural sinus thrombosis on MRI. No pre-existing risk factors were identified in patients of this group. The difference between the two groups was not statistically significant (*Z value 0.545, p value 0.582*).

Chronic findings and normal MRI study: Forty one (41/84, 49%) studies in COVID-19 positive group showed chronic findings as compared to 194/323 (60%) in the COVID-19 negative subgroup. Of particular note is microhemorrhages, which have multifactorial etiology including amyloid and hypertensive microangiopathy was classified as chronic finding. 15/84 (17.9%) patients in COVID-19 positive group had normal MRI findings as compared to 86/323 (26.6%) in the COVID-19 negative group. These differences in chronic findings and normal MRI variables were statistically insignificant (*Z value = -1.859, p value = 0.0629 and Z value = -1.657, p value = 0.969* respectively)

Imaging findings are summarized in Table 2.

Mortality

5/24 (20.8%) patients in COVID-19 positive group with acute MRI abnormality did not survive the disease, whereas, this figure was 9/59 (15.2%) in the COVID-19 negative group. This difference was not found to be statistically significant (*Z = -0.615, p= 0.535*)

DISCUSSION

The current case-control study compares MRI abnormalities between COVID-19 positive

Table 2: Summary of MRI findings in COVID-19 positive and COVID-19 negative groups with result of the Z-test for two population proportions analysis of imaging features between two groups

	COVID-19 positive	COVID-19 negative	Z-value	p- value
	n/N	**n/N**		
1. Acute infarction	15/84	34/323	1.839	0.065
a. Large vessel	04/15	09/34	0.014	0.992
Hemorrhagic	01/04	01/07	0.64	0.522
b. Small vessel	07/15	18/34	-0.405	0.689
Hemorrhagic	02/07	02/18	1.069	0.285
Multifocal	02/07	03/18	0.668	0.502
c. Embolic	04/15	07/34	0.47	0.638
2. Acute Intracranial hemorrhage	04/84	14/323	0.170	0.865
a. Parenchymal	03/04	10/14	0.141	0.889
b. Subarachnoid	00/04	02/14	-0.802	0.424
c. Extra-axial	01/04	02/14	0.507	0.610
3. Acute diffuse white matter encephalopathy	02/84	01/323	**1.977**	**0.047**
4. Intracranial infection	02/84	08/323	-0.050	0.960
5. Dural sinus thrombosis	01/84	02/323	0.545	0.582
6. Chronic findings	41/84	194/323	-1.859	0.0629
7. Normal MRI	15/84	86/323	-1.657	0.969

*p value ≤ 0.05 is considered significant

and COVID-19 negative patients with acute neurological symptoms without statistically significant difference in age or co-morbidities.

Acute infarction: In the COVID-19 group, 23/84 (28.6%) patients had acute findings on MRI brain, which is higher than previous study by Yoon *et al*.[11] and lower than in the study by Mahammedi *et al*.[8] Acute ischemic stroke 15/24 (62.5%) was the most common MRI finding in this study which is consistent with all previous studies, however there is a wide variation in the frequency among all studies (15%-50%).[11,12] A study by Benny *et al*.[18], done in similar population also reported comparable incidence of moderately severe and severe strokes (National institute for health stroke scale/score) in their COVID-19 positive and COVID-19 negative groups. They however reported a positive correlation between large vessel occlusive stoke and COVID-19 infection which was not seen in our study. The difference in mild and moderate stroke severity may be attributable to the severely affected region in which their study was carried out. In our geographical region, there was no scarcity of medical care owing to lesser number of COVID-19 cases in the first COVID wave, which may have resulted in better confidence of COVID-19 negative mild stroke patients seeking hospital care.

Acute intracranial hemorrhage: The frequency of intracranial hemorrhages 4/24 (16%) was lower in our study as compared to the study by Yoon *et al*. (42%)[11] as we did not include microhemorrhages as acute neurological finding due to its multifactorial etiology, especially in older age group (mean age 63.3 years). Frequency of acute intracranial hemorrhage reported in our study (4/24,16%) is however higher than that reported by Mahammedi *et al*. (6%)[8] and is comparable to Sawlani *et al*. (10%)[12] and Benny *et al*.[18] (9%).

Acute diffuse white matter encephalopathy: Acute diffuse leukoencephalopathy have been described in patients with COVID-19 infection.[19,20] The frequency of acute diffuse white matter encephalopathy in our study (2/84, 2.4%) was much lower than studies by Yoon *et al*. (27%)[11] and Mahammedi *et al*. (35%)[8], but was comparable to the study by Sawlani *et al*. (5%).[12]

Intracranial infection: The reported infections in our study in both groups were comparable 2.4 % in COVID-19 positive group and 2.5 % in COVID-19 negative group. Previous studies [8,11,12,14] did not report any cases of intracranial infection. We also attribute it to chance occurrence rather than a direct causal relationship.

Dural sinus thrombosis: The only patient in COVID-19 positive group had a pre-existing co-morbidity which can be directly linked to dural sinus thrombosis. This was not statistically different from the COVID-19 negative group.

Mortality: Mortality was higher in the COVID-19 positive group (20.8% vs 15.2%); however, this was not significant statistically. This was in agreement with previous study by Benny *et al*.[18] We attribute the differences in incidence of MRI abnormalities to geographical / population differences and study design.

We found a weak association between COVID-19 infection and acute diffuse white matter encephalopathy. This may be related to an obvious hypoxic state in COVID-19 pneumonia as compared to the COVID-19 negative group.

In our study, there was a statistically significant difference in altered coagulation in COVID-19 patients as compared to the COVID-19 negative controls, but we did not observe a significant increase in incidence of acute ischemic complications or intracranial bleed attributable to it. Rest of the epidemiological factors and co-morbidities were comparable in both groups. Moreover, at our institution, all patients underwent RT-PCR for SARS-CoV-2 before admission, so, asymptomatic patients were also classified into the COVID-19 group, who may not have had COVID-19 related neurological disease. This further dilutes the number of subjects in COVID-19 positive subgroup.

The limitations of our study are first, it focuses on patients presenting with acute neurological symptoms which may not be representative of sedated / subconscious patients admitted in intensive care. Another limitation of our study is small number of cases in the COVID-19 positive group.

In conclusion, the current case control study points towards a weak direct association between COVID-19 infection and acute abnormalities in MRI brain studies, especially in patients with pre-existing co-morbidities. More case-control studies are required in future for further validation of these findings.

DISCLOSURE

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