Emergent Large Vessel Occlusion in Ischemic Stroke in SARS-COV-2 Virus (Severe Acute Respiratory Syndrome Corona Virus 2) Pandemic: An observational analytical study on proportion

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Abstract

Background and aim: Various neurological manifestations have been described with COVID-19 infection after it first appeared in 2019. Increased risk of strokes secondary to a hypercoagulable state is now well identified. In this study, we analysed the proportion of large vessel occlusions in patients with COVID-19 admitted at our hospital occurring before and during the COVID-19 pandemic to ascertain whether SARS-CO-2 Virus infection has a tendency to provoke thrombotic tendency. **Methods:** It was an observational study done retrospectively at Bharati Hospital and Research Centre (BHRC), Pune. We measured the proportion of large vessel occlusion before and after the onset of the Covid 19 pandemic. **Results:** A total of two hundred and seventy-six patients (191 female and 85 male) were identified during the study period. The mean age of the patients was 57±15 years. Of these (n=276), a total of 144 (52.2%) had large vessel occlusion, while 132(47.8%) had small vessel occlusion. Of the patients with large vessel occlusion, 52.78% had a history of hypertension, 40.28% had a history of diabetes mellitus, and 19.45% had a history of cardiac disease. In the pre-pandemic period, 43 (41.7%) patients had large vessel occlusion, while this number rose to 101 (58.4%) during the pandemic period (p=0.007). In the pre-pandemic period, 7.8% of patients succumbed to the stroke by the 10th day of admission, while during the pandemic period, 6.3% of patients succumbed to the stroke (p= 0.655). **Conclusion:** Emergent Large vessel occlusions were significantly higher during the pandemic period as compared to the pre-pandemic period. Further studies are required to examine this association and the pathophysiological mechanisms of stroke in COVID-19 patients.

Introduction

Coronavirus disease (COVID-19) occurs due to infection of the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2). It was first described in Wuhan, China but rapidly spread across the entire world. The disease was new to clinicians across the world, and it was initially primarily thought to involve the respiratory system. However, reports soon emerged describing a wide variety of multi-system involvement. Several neurological manifestations were soon reported. The cerebrovascular disease has been reported with a frequency of 2.8-5.7% in a systematic review by Munhoz et al.[(1)]. In a study by Majhidi et al. in New York, a 2-fold increase was found in the number of large vessel occlusion patients compared to the same period the year prior and in the past 15 months before the outbreak[(2)]. It has been postulated that a hypercoagulable state due to the activation of the cytokine cascade ultimately leads to vascular thrombosis [(2)]. Other postulated mechanisms include direct cardiac injury, endothelial injury, vasculitis, cytokine storm, micro-vascular thrombosis, etc.[(2, 3)]. We conducted this study aiming to find any association between large vessel occlusion and COVID-19.

Material and Methods

It was an observational study done retrospectively at Bharati Hospital and Research Centre (BHRC), Pune. BHRC is a tertiary care NABH accredited 836 bedded hospital in the South of Pune Municipal Corporation. Clearance was obtained from the institutional ethical review committee. All patients aged more than 12 years admitted with stroke at BHRC, Pune were included in this study. The study period was from October 2019 to September 2021. The study has two phases, the first phase included group of patients who presented with stroke before the pandemic of COVID-19 began, i.e., till February 2020. The second phase was group of patients who presented with stroke after March 2020. Only those patients who were Real Time Polymerase Chain Reaction (RT-PCR) positive for COVID-19 were included in the second group. Large vessel occlusion was suggested by stroke severity at onset and National Institute of Health Stroke Scale (NIHSS) score of more than 8, a pearl of string sign on Diffusion Weighted Magnetic Resonance Imaging (DWMRI) or Computed Tomography (CT) or Magnetic Resonance (MR) imaging showing infarct in territory involving Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA) or Posterior Cerebral Artery (PCA) territories. Angiography was not possible in the pandemic period for all patients due to logistical issues in the hospital. Hence, angiography was done only in selected patients eligible for contrast injection and stable enough to be shifted to the radiology department. For the rest of the patients, the presence of large vessel occlusion was assumed indirectly based on proven clinic-radiological findings as mentioned above. We assessed demographic data and the presence of risk factors for stroke in both groups. The proportion of large

vessel occlusions before and after the COVID-19 pandemic began was assessed. Appropriate statistical analysis tests were applied for data using SPSS software. We measured the proportion of large vessel occlusion before the COVID-19 pandemic began compared to the proportion during the pandemic.

Results

A total of 103 cases (37.3%) of stroke were admitted at the hospital before the pandemic began, while 173 cases (62.7%) of stroke were admitted at the hospital during the pandemic (Total 276) (See Table 1). A total of two hundred and seventy-six patients (191 female and 85 male) were identified during the study period starting from October 1, 2019, to September 30, 2021.

Table 1: Demographics of the study population

	Total	Pre-Pandemic Period	Pandemic Period	p value
Age, Mean (± SD)	57.5 (15.5)	59.7(15.5)	56.1(15.4)	0.062
Gender	276	103	173	
Female, n (%)	191 (69.2)	66 (64.1)	125 (72.3)	0.155
Male, n (%)	85 (30.8)	37(35.9)	48(27.7)	
Blood Pressure (SBP), Mean (± SD)	146.3(29.2)	147.9(25.3)	145.3(31.4)	0.279
Blood Pressure (DBP), Mean (± SD)	86.9(14.5)	87.8(12.9)	86.3(15.3)	0.315
Past medical history				
Hypertension (HTN), n (%)	153 (55.4)	51 (49.5)	102 (59.3)	0.127
Old Cerebral Vascular Accident (CVA), n (%)	28 (10.1)	8 (7.8)	20 (11.6)	0.313
Diabetes Mellitus (DM), n (%)	116 (42.2)	45 (43.7)	71 (41.3)	0.666
Cardiac disease, n (%)	42 (15.2)	17 (16.5)	25 (14.5)	0.646
Tobacco, n (%)	18 (6.5)	7 (6.8)	11 (6.4)	0.887
Alcohol, n (%)	10 (3.6)	7 (6.8)	3 (1.7)	0.03
Homocysteine(micromole/lt), n (%)	96 (34.8)	29 (28.2)	67 (38.9)	< 0.001
Vital status at day 10: dead, n (%)	19 (6.9)	8 (7.8)	11 (6.3)	0.655
Laboratory parameters				
Total Cholesterol, Mean(± SD)	183.9(54.8)	187.7(49.1)	181.9(57.6)	0.433
High Density Lipoprotein (HDL) (mg/dl), Mean (± SD)	35.3(8.9)	33.8(7.3)	36.1(9.6)	0.209
Low Density Lipoprotein (LDL) (mg/dl), Mean (± SD)	121.5(42)	123.3(37.6)	120.5(44.3)	0.525
Triglyceride Levels (TGL) (mg/dl), Mean (± SD)	144.1(96)	154.4(108.9)	138(88.9)	0.599
Very Low Density Lipoprotein (VLDL), Mean (± SD)	28.7(18.9)	30.7(21.8)	27.7(17.2)	0.568
Haemoglobin(g/dl), Mean (± SD)	13(2.6)	12.5(2.7)	13.1(2.5)	0.165
Platelets (lakhs/dl), Mean (± SD)	255039(97880)	275932(94822)	245017(98117)	0.027
Blood urea, Mean (± SD)	27.6(18.8)	27.4(19.9)	27.7(18.3)	0.697
Serum Creatinine (mg/dl)	1.6(5.9)	1.3(2.3)	1.7(7.1)	0.685
Vessel occlusion				
Small Vessel Occlusion (SVO), n (%)	132 (47.8)	60 (58.3)	72 (41.6)	0.007
Large Vessel Occlusion (LVO), n (%)	144 (52.2)	43 (41.7)	101 (58.4)	

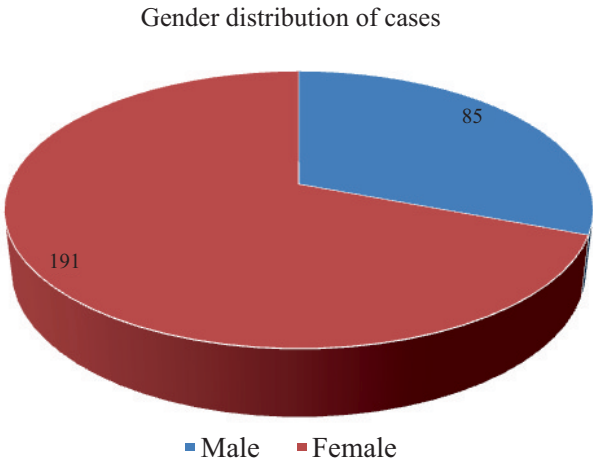

Fig 1: Gender distribution of 276 cases of Ischemic Stroke with large vessel Occlusion

These (n=276), a total of 144 (52.2%), had large vessel occlusion while 132(47.8%) had small vessel occlusion. The mean age of the patients was 57±15 years. Of the total patients, 55% patients had a history of hypertension, 42.2% had a history of diabetes mellitus, 15.2 % had a history of cardiac disease, and 10.1% had a history of prior stroke. Hyperhomocysteinemia was present in about 34.8% of the patients. About 6.5% of patients reported chewing tobacco, while 3.6% reported alcohol intake. Of the patients with large vessel occlusion, 52.78% had a history of hypertension, 40.28% had a history of diabetes mellitus, and 19.45% had a history of cardiac disease. Other laboratory parameters related to the study population are present in **Table 1**. COVID was indirectly suspected in 173 patients based on their clinical symptoms and established guidelines at the initial phase of the pandemic. Out of 276 patients, 103 patients were in the pre-pandemic period and 173 patients in the pandemic period. Small vessel occlusion was seen in 132 patients, of which 60 (58.3%) were in the pre-pandemic period, and 72 (41.6%) were in the pandemic period. Whereas Large Vessel Occlusion overall was 144 patients, in which 43(41.7%) were in the pre-pandemic and had increased to 101 (58.4%) in the pandemic, which is statistically significant. The mean age of COVID positive patients was lower (49.8 ±15.3) than COVID negative patients (56.7±15.3, p=0.21) (Table 2).

In the pre-pandemic period, 43 (41.7%) patients had large vessel occlusion, while this number rose to 101 (58.4%) during the pandemic period (p=0.007). In the pre-pandemic period, 7.8% of patients succumbed to the stroke by the 10th day of admission, while during the pandemic period, 6.3% of patients succumbed to the stroke (p= 0.655). COVID patients showed LVO more often due to large friable thrombi, and with treatment, they were corrected without sequelae, unlike the ischemic strokes secondary to underlying atherosclerotic and cardioembolic mechanisms.

Table 2: Demographic characteristics of patients with COVID positive versus COVID negative status

	Total	COVID Positive	COVID Negative	p value
Age, Mean (+SD)	56.7(15.3)	49.8(15.3)	56.7(15.3)	0.121
Gender, Female, n (%)	125 (72.3)	2 (15.4)	46 (28.7)	0.301
Blood Pressure (SBP), Mean (±SD)	147.4(31)	119.2(24)	147.4(31)	0.002
Blood Pressure (DBP), Mean (±SD)	87.2(15.3)	75.4(10.5)	87.2(15.3)	0.007
Past medical history				
HTN, n (%)	102 (59)	3 (23.1)	99 (61.9)	0.007
Old CVA, n (%)	20 (11.6)	3 (23.1)	17 (10.7)	0.177
DM, n (%)	71 (41)	5 (38.5)	66 (41.3)	0.544
Cardiac disease, n (%)	25 (14.5)	1 (7.7)	24 (15)	0.411
Tobacco, n (%)	11 (6.4)	1 (7.7)	10 (6.3)	0.588
Alcohol, n (%)	3 (1.7)	1 (7.7)	2 (1.3)	0.21

Table 2: Continued...

Laboratory Parameters	Total	COVID Positive	COVID Negative	p value
Total Cholesterol, Mean (±SD)	182.9(57.9)	140(11.3)	182.9(57.9)	0.301
HDL (mg/dl), Mean (±SD)	36.4(9.5)	24(12.7)	36.4(9.5)	0.073
LDL (mg/dl), Mean (±SD)	121.1(44.7)	98.5(0.7)	121.1(44.7)	0.48
TGL (mg/dl), Mean (±SD)	140.1(89.6)	84(4.2)	140.1(89.6)	0.381
VLDL, Mean (±SD)	27.9(17.3)	16.5(0.7)	27.9(17.3)	0.356
Haemoglobin (g/dl), Mean (±SD)	13.1(4472.8)	14.3(2.9)	13.1(2.6)	0.262
Platelets (lakhs/dl), Mean (±SD)	246414.7(347410.7)	221857.1(126362.5)	246414.7(96670.9)	0.522
Blood urea, Mean (±SD)	28.1(4569.9)	21.1(13.2)	28.1(18.6)	0.332
Serum Creatinine (mg/dl), Mean (±SD)	1.8(4595.7)	0.9(0.2)	1.8(7.3)	0.738
Vessel occlusion				
SVO, n (%)	72 (41.6)	2 (15.4)	70 (43.8)	0.04
LVO, n (%)	101 (58.4)	11 (84.6)	90 (56.3)	

Discussion

The prevalence of large vessel occlusion in non-COVID cases is estimated to be 20-38%[4]. Several studies have emerged during the COVID-19 pandemic suggesting an increase in large vessel occlusions. Our study has reflected similar observations. In the pre-pandemic period, 43 (41.7%) patients had large vessel occlusion, while this number rose to 101 (58.4%) during the pandemic period (p=0.007). In a study done in New York, 50% of the patients of LVOs were positive for COVID-19 compared to the 19.9% infection rate in the general population in New York[2]. In a case-control study from New York, among a total of 329 patients for whom code stroke was activated, 116 (35%) were found to have an acute ischemic stroke on imaging. Of these, 71 (21.6%) were found to have LVO, while 48 (14.6%) were found to have Small Vessel Occlusion. In this study, LVO was present in 31.7% of those with COVID compared with 15.3% of patients without COVID (p=0.001)[5]. In another study from the middle east (n= 20), LVO was found in as much as 75% of the patients[6].In a multicentre study involving 6698 patients in 9 stroke centres by Khandelwal et al., the incidence of LVO was 60%. The majority of patients in the LVO cohort presented in the emergency room (81%), while some (19%) presented during hospitalization. The reperfusion rate (TICI >2b) of the LVO cohort in this study was 81%. The rate of discharge to home or rehabilitation facilities was found to be 50%[7].

Several mechanisms have been postulated to increase the number of LVOs in patients with COVID. However, the pathophysiological mechanisms involved in coagulation in COVID-19 are different from conventional sepsis-induced coagulopathy. The cytokine storm occurring in COVID-19 is more severe and results in widespread microvascular and macrovascular thrombosis and end organ failure[8,9]. The key differences observed in COVID-19 related coagulopathy include absent or mild thrombocytopenia, modest consumption of coagulation factors, and absence of red blood schistocytes[9]. One of the key activators of coagulopathy in severe COVID-19 is IL-6 (Interleukin-6). It induces tissue factor expression and increased platelet and fibrinogen production. Hypoxia and dysregulation of the urokinase pathway have also been implicated in the more severe coagulopathy encountered in COVID-19[9]. These contribute to the macrovascular thrombosis seen in COVID-19. In addition, microvascular thrombosis has also been described, especially in the pulmonary vasculature. A high incidence of pulmonary thromboembolism was found in an autopsy series by Lax et al.[10]. High fibrin formation and degradation levels, intense complement activation, platelet aggregation, formation of platelet-fibrin complexes, and endothelial injury are the various mechanisms proposed for microvascularthrombosis[9]. In line with the above, elevated D-dimer levels have been reported to be a strong predictor of the severity and prognosis of the disease[8]. As expected, anticoagulation treatment mainly with low molecular heparin appears to be associated with a better prognosis[11].

There are limitations to our study. In the early period of the pandemic, there was limited availability of RT-PCR testing in India. A single centre was available in our city, and it was a national centre with a very high load of tests being run daily. As a result, PCR testing was not possible in all patients, and patients were admitted based on clinical features and as per national guidelines. CT angiography was not possible in all our COVID-19 patients due to logistical issues. We diagnosed the presence of large vessel occlusion based on clinic-radiological findings. Secondly, D-dimer level

measurement was not a routine test done in the pre-pandemic period and hence was not available for comparison. As our centre was a tertiary referral center for COVID-19 management, the rise in the number of LVO strokes could also be due to referral bias.

Conclusion

Large vessel occlusions were significantly higher during the pandemic period as compared to the pre-pandemic period. Further studies are required to examine this association and the pathophysiological mechanisms of stroke in COVID-19 patients.

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