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Short Communication

Management and Outcomes of COVID − 19 Associated Cerebral Venous Sinus Thrombosis

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Background: Systemic hyper-coagulabilty leading to micro and macro thrombosis is a known complication of Coronavirus disease − 2019(COVID -19). The postulated mechanism appears to be the viral activation of endothelium, triggering the coagulation pathways. Thrombosis of the cerebral veins and sinuses (CVT), a potentially serious condition, has been increasingly reported with COVID − 19 infection. In this clinical study we attempt to describe the clinical profile, investigations and outcomes of patients with COVID- 19 associated CVT. *Methods:* This is a single center prospective observational study from South India. The study included patients (aged >18 years) with concomitant COVID infection and CVT. The clinical, laboratory, imaging characteristics, management and outcomes were described and compared with COVID negative CVT patients. *Results:* Out of 97 cases of CVT treated at our center during the first and second waves of the COVID pandemic 11/97 (11%) were COVID related CVT. Among these 11 patients, 9 (81%) had presented with only CVT related symptoms and signs and were tested positive for COVID - 19 infection during the pre-hospitalization screening. Respiratory symptoms were absent in 90% of the patients. Headache (100%) and seizures (90%) were the common presenting symptoms. The median time to diagnosis was 6 hours, from presentation to the emergency department. Transverse sinus was involved 10/11 (90%) and majority of them (9/11) had Haemorrhagic Venous Infarction (HVI). Acute inflammatory markers were elevated in comparison with non COVID CVT patients, with the mean serum D-dimer being 2462.75 ng/ml and the C-reactive protein was 64.5 mg/dl. Three patients (30%) underwent decompressive hemicraniectomy (DHC) because of large hemispheric HVI. All patients survived in the COVID CVT group while the mortality in the non COVID group was 4%. At 6 months follow up excellent outcome (modified Rankin Scale (mRS) score of 0−2) was noted equally in both groups. *Conclusions:* Symptoms and signs of CVT may be the only presentation of COVID-19 infection. Prompt recognition and aggressive medical management including DHC offers excellent outcomes.

Key Words: COVID-19—Cerebral venous thrombosis—Decompressive hemicraniectomy

Introduction

Since March 11, 2020, the world has been grappled by the pandemic caused by the novel severe acute coronavirus − 2(SARS-CoV2) with varied system-specific manifestations and guarded outcomes. Thrombotic complications have been increasingly reported in critically ill COVID patients.[1] This virus stands unique in comparison to other respiratory viruses, in view of its direct infection of endothelial cells with abnormal macrophage activation, and recruitment of peri-vascular T-cell infiltrates causing endothelial and inflammatory cell death, thrombotic microangiopathy, and angiogenesis.[1] This seems to be potentiated by a state of hypercoagulability caused by increased concentrations of coagulation factors, acquired antiphospholipid antibodies, and decreased concentrations of endogenous anticoagulant proteins.[2] Cerebral venous sinus thrombosis (CVT) as a presenting symptom in COVID-19 disease was first reported by Hughes et al.

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in April 2020.[3] Since then, there have been multiple case reports and case series published, describing the occurrence of CVT in context with infection as well as with vaccination. Despite the best management, the mortality remains high, which ranges from 20% to 40%, making this a neurological complication which calls for a prompt identification and initiation of early aggressive management.[4–6] In this short report, we present our experience in management of patients with COVID- 19 associated CVT, across the two waves of the pandemic (2020−2021), describing the clinical presentation, the thrombotic derangements, management and outcomes in these patients and comparing them with the non COVID CVT patients managed during the same time period. To the best of our knowledge, this is the first report on outcomes, post decompressive hemicraniectomy (DHC) among patients with COVID − 19 associated CVT.

Methods

The study was conducted in Christian Medical College, Vellore a tertiary care referral Center in South India. Patients aged 18 years or above with recent COVID-19 infection, confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab for COVID-19, were included. The diagnosis of CVT was confirmed by magnetic resonance imaging with venography (MRI and MRV). CVT patients with confirmed COVID − 19 were taken as cases, and CVT patients who were tested negative and treated during the same period were taken as controls. The risk factors, clinical features, laboratory findings, radiological findings, COVID-19 disease status, and data on management and outcomes for all patients were described and compared between the cases and controls. The primary outcome was the mortality rate and proportion with good functional outcome at discharge as defined as a score of ≤ 2 in the Modified Rankin' disability scale (mRS). History of COVID vaccination was noted and any vaccine associated CVT cases were excluded.

Results

There were 2 waves of pandemic in India, the first wave peaked between September and October 2020, the second being in March−April 2021. About 52 cases of CVT were admitted during the first wave, and about 45 cases were hospitalized during the second wave. Among these, 11 patients had concomitant COVID infection and CVT.

Clinical features and investigations including imaging characteristics

The mean age appeared to be the third decade with male preponderance. Antecedent thrombotic risk factors were less in both the cases and controls. All of them reported headache and seizures were more common in the COVID group. CVT as an index presentation of COVID − 19 was seen in 81% (n = 9). Typical influenza like illness (ILI) was reported only in 2 patients with COVID positivity. One patient was critically ill with acute respiratory distress syndrome requiring mechanical ventilation. About 11 patients in the non COVID group reported respiratory symptoms, however they were tested negative. Hemorrhagic venous infarction (HVI) was seen in 81%, in the COVID positive group vs. 40% in the COVID negative group and in both the groups it predominantly involved the temporal lobe. The COVID positive patients expressed higher inflammatory markers, aPL antibody positivity and thrombotic markers, which was statistically significant when compared to the non COVID controls. The clinical, laboratory, imaging characteristics with outcomes are tabulated in Table 1.

Management and outcomes

The median time of symptoms prior to presentation was 5 days (IQR 2 − 10). The median time to diagnosis of CVT, from the time of presentation to emergency department was 6 hours (IQR 4 − 28). All patients were treated with therapeutic anticoagulation, anti-epileptic drugs and antiedema measures with oral acetazolamide and hypertonic saline infusions. Three patients underwent emergency DHC in the COVID group as opposed to 5 patients in the non − COVID group, within 24 h of presentation. There was no mortality in our cohort of COVID positive group, all patients improved on therapy, and were discharged, however 3 patients died in the non COVID group at discharge, and 1 more at 3 month follow-up.

Follow − up data was available for 89 patients with CVT, treated during the two waves of the pandemic at 3 months and 87 patients at 6 months follow-up. In the COVID positive CVT group, the proportion of patients with good clinical outcome (mRS≤2) at was 81% at discharge and 90% at 6 months. The functional status at follow − up in comparison with the COVID negative controls are shown in Fig. 1. Among the 3 patients who underwent decompressive hemicraniectomy, 2 patients had good clinical outcome and 1 patient continued to be in minimally conscious state (Fig. 2).

Discussion

This study is one among the large case series from a single center, involving the Indian population with COVID 19 and CVT. Our Center, a quaternary care referral hospital in South India, deals with high burden of patients presenting with CVT.[7] It is striking to note that the CVT was the presenting symptom for COVID -19, and the classical ILI symptoms were seen only in 2 patients. We could have missed out diagnosing COVID infection in the remaining, but for the institutional policy of admission only after screening for COVID infection during the pandemic period. Hameed et al. in their case series, reported

Table 1. *Clinical, laboratory, imaging characteristics and outcomes.*

Clinical Characteristics	COVID positive(n = 11)	COVID negative (n = 86)	
Age(mean, IQR yrs)	35(19−45)	38(18−68)	
Male gender	60%	60%	
Pre − existing conditions			
Hypertension	9%	17%	
Diabetes Mellitus	9%	13%	
OCP use	0	7%	
HIV infection	9%	1%	
Malignancy	0	0	
Postpartum	18%	1%	
Symptoms			
Respiratory symptoms	9%	11%	
Headache	100%	82%	
Seizures	90%	29%	
Focal Neurological deficits	72%	98%	
COVID − 19 severity status			
Asymptomatic	81%	-	
Mild	0	-	
Moderate	9%	-	
Severe	9%	-	
GCS at admission(IQR)	11(8−15)	13(3−15)	
Laboratory parameters			***P* value**
Haemoglobin (mg%±SD)	12.4(2.9)	14.6(3.8)	0.78
C Reactive Protein (mg/dl± SD)	64.5(57.8)	23.05(33.5)	<**0.001**
D- Dimer (ng/ml±SD)	2462.7(1909)	1074.1(1234)	**0.052**
Homocysteine (μmol/l±SD)	17.7(19.1)	65(15.3)	**0.003**
Decreased Protein C (%)	14.2	2.3	**0.042**
Decreased Protein S (%)	0	2.3	**-**
APCR (%)	57.1	4.6	<**0.001**
Elevated factor VIII (%)	42.8	24.4	**0.052**
Apl antibody positivity (%)	27	5	**0.032**
Imaging characteristics			
Hemorrhagic venous infarction (%)	81%	40%	**0.024**
Superior sagittal sinus	63%	67%	**-**
Transverse sinus	90%	66%	**-**
Sigmoid sinus	72%	55%	**-**
Deep venous system	18%	6%	**-**
Treatment modalities			
Only medical management	70%	95%	**-**
Mechanical thrombectomy	0	0	**-**
Decompressive hemicraniectomy	30%	5%	**-**
Outcomes			
Mortality (%)	0%	4%	**-**
Good functional status at 6 months (mRS<2)	90%	79%	**-**

yrs - years, IQR - Inter Quartile Range, OCP - Oral contraceptive pills, HIV - Human Immunodeficiency Virus, GCS - Glasgow Coma Scale,APCR - Activated Protein C Resistance, Apl − Antiphospholipid antibodies, SD − Standard deviation, mRS- modified Rankin's scale

55% of the subjects having ILI symptoms.[5] In a systematic review and meta-analysis by Baldini et al. including 57 cases from 28 reports, 92.9% were symptomatic for COVID − 19 with 81% having abnormal lung imaging and in 90% of the cohort, CVT occurred with/after symptom onset.[4] High prevalence of Antiphospholipid antibodies(aPL) have been reported in hospitalized COVID patients(73.3%).[8] In a systematic review and metanalysis by Taha and Samavati, nearly half of patients with COVID-19 were positive for one of the aPL, most frequently reported aPL being lupus anticoagulant.[9] They occur more frequently in critically ill patients and were not significantly associated with disease outcomes like venous thrombosis, invasive ventilation and mortality. Similarly, in our series the presence of aPL antibodies, decreased protein C, activated protein C resistance (APCR) and elevated factor 8 levels might be a consequence of endothelial activation and inflammation.

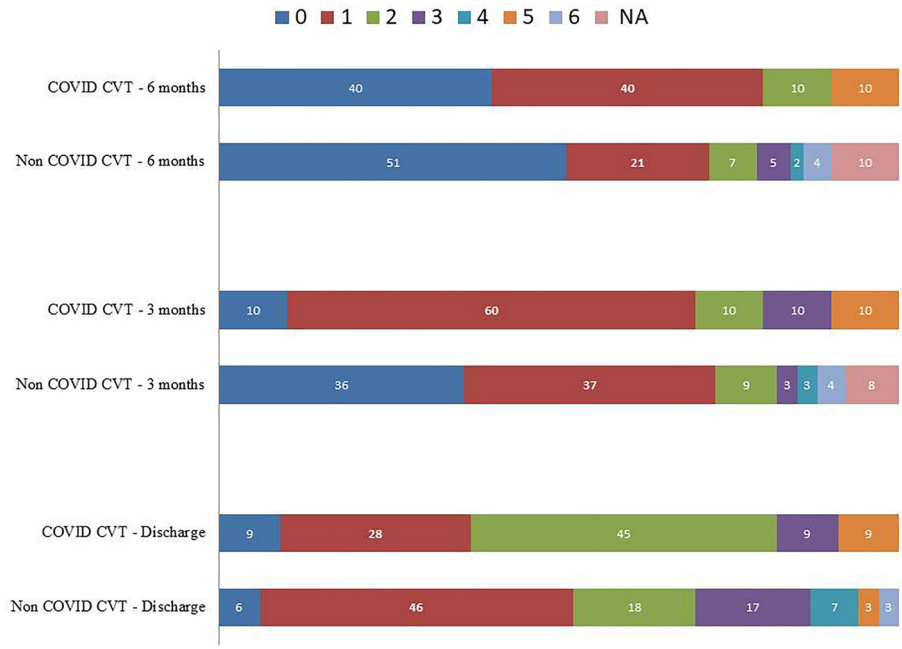

Fig. 1. *Functional outcomes of COVID associated CVT and non COVID CVT at discharge, 3 months and 6 months.*

The most salient finding in this study is the outcomes, which includes no mortalities in the COVID group and 4% in the non COVID group with good functional outcomes at discharge and at 6 month follow- up. This could be partly due to rapidity in diagnosis (median time − 6 h from presentation) and initiation of early aggressive therapy in the form of hydration, therapeutic anticoagulation and anti-edema measures. Published evidence have varied mortality rates between 10% and 40% (Tu et al., 2020),[4–6] with presence of parenchymal bleed being an important predictor of mortality. Despite the presence of parenchymal bleed in 80% of our cohort, the uniformly good outcomes emphasise the importance of prompt recognition and management.

Offering surgical management like DHC, in the setting of COVID -19 infection is a challenging situation for the neurologists and neurosurgeons. There are various considerations including the risk of worsening respiratory status, progression of multi − organ dysfunction, need for prolonged intensive care and the risk to the healthcare professionals. To − date there have been only 8 cases of DHC in COVID − 19 patients with malignant ischemic anterior circulation infarction, where 3 were discharged and mortality rates exceed 33%.[10,11] Our previous experience in DHC among patients with CVT, have proven to have excellent outcomes.[12] Similarly prompt decision to DHC in the 3 patients in COVID cohort, within 24 h of admission has resulted in good functional outcomes in 2 patients. The patient, who continued to be with persistent low sensorium, had other comorbidities like HIV infection and diabetes which might have contributed to the morbidity despite the aggressive management.

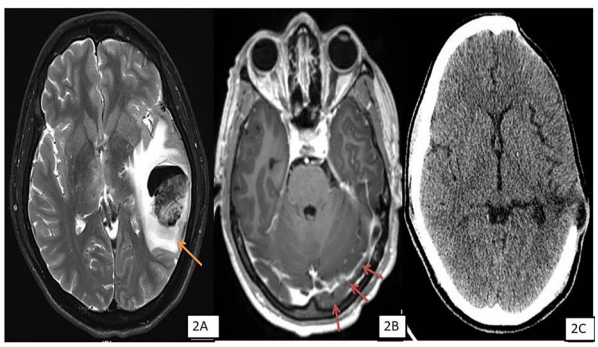

Fig. 2. *50 year old gentleman with COVID infection, new onset seizures and right hemiparesis, 2A - Left temporal haemorrhagic venous infarct, 2B - Thrombosis of transverse sinus, 2C - Status post DHC, at discharge with resolved edema and mass effect.*

Conclusions

CVT could be the index presentation of COVID 19 infection without the presence of ILI symptoms. COVID-19 testing should be included as standard workup for all CVT patients as 11% of CVT cases treated during the pandemic were related to COVID; also all COVID-19-positive patients with headache and neurological symptoms should be evaluated for CVT. Prompt recognition with aggressive medical management alleviates mortality. DHC should be offered, if required early into the course of illness, despite a positive test for COVID − 19.

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