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Comparative Study of Cerebral Venous Thrombosis-Risk Factors, Clinical Course, and Outcome in Subjects with and without COVID-19 Infection

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Keywords

Cerebral venous thrombosis · Coronavirus disease 2019 · Risk factors · Demographics · Outcome

Abstract

Background/Objective: Cerebral venous thrombosis (CVT) has been increasingly reported in patients with COVID-19. Most published literature is descriptive and focuses only on CVT in COVID-19 patients. The objective of our study was to compare CVT patients' characteristics with and without an associated COVID-19 infection. ***Materials and Methods:*** This is a retrospective cross-sectional study. All adult patients with a confirmed diagnosis of CVT admitted to our hospital over a period of 30 months, from January 2019 to June 2021, were included. They were further divided into two groups, with and without COVID-19 infection. ***Results:*** A total of 115 CVT patients were included, 93 in non-COVID-CVT and 22 in COVID-CVT group. COVID-CVT patients were male predominant and of older age, with longer hospital stay, and higher inpatient mortality. COVID-CVT patients presented with a higher frequency of headache (82% vs. 63%), seizures (64% vs. 37%, $p = 0.03$), hemiparesis (41% vs. 24%), and visual changes (36% vs. 19%) as compared to non-COVID-CVT patients. Venogram showed a higher frequency of superior sagittal sinus (64% vs. 42%) and internal jugular vein (23% vs. 12%) involvement in the COVID-CVT cohort. More than 90% of patients in both groups received therapeutic anticoagulation. Mortality rates were higher in COVID-CVT group (18% vs. 11%). ***Conclusion:*** COVID-CVT patients were male predominant and of older age, with higher hospital stay, and higher inpatient mortality as compared to non-COVID-CVT patients.

Introduction

Cerebral venous thrombosis (CVT) is an uncommon neurological vascular condition, which has been increasingly reported in patients with coronavirus disease 2019 (COVID-19) [1–7]. Previously, we reported 20 cases of CVT with COVID-19 in four Asian countries [3]. Other similar studies have described the characteristics of this cohort of patients with CVT and COVID-19 [5–7]. Since most of these studies have only focused on COVID-19 patients having CVT, there is a lack of comparative data.

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The objective of our study is to compare CVT patients' characteristics with and without an associated COVID-19 infection in our population. An Indian study has previously compared the characteristics of patients with a diagnosis of CVT in COVID-19 and non-COVID-19 populations at their center [6].

Materials and Methods

We conducted a retrospective cross-sectional analysis of hospital records using a prespecified questionnaire. All the adult patients, >18 years of age, with a confirmed diagnosis of CVT admitted to our hospital over a period of 30 months, from January 2019 to June 2021, were included in this study. CVT diagnosis was confirmed by the presence of a thrombus in cerebral venous vasculature by at least one of the following imaging studies according to the established criteria: MRI, MRV, CT, or CTV, reported by an experienced neuroradiologist.

The CVT patients were divided into two groups, with and without COVID-19 infection. CVT patients with a positive nasopharyngeal swab polymerase chain reaction (NPS-PCR) testing for the SARS-CoV-2 virus during admission or 90 days prior to the diagnosis of CVT were included in the COVID-CVT group, while CVT patients diagnosed before February 26, 2020 (the first reported case of COVID-19 in Pakistan [8]), as well as CVT patients with negative NPS-PCR for the SARS-CoV-2 virus, were grouped into non-COVID-CVT. Exclusion criteria include an absence of NPS-PCR testing (after February 26, 2020), chest imaging suspicious of COVID-19 infection, head trauma, and vaccine-related CVT.

The data obtained included patient demographics, clinical symptoms, diagnostic imaging, COVID-19 status, hospital treatment received, and modified ranking scores for both COVID and non-COVID-CVT cases. All the data were analyzed on the SPSS software.

Results

A total of 134 patients were diagnosed with CVT during our eligibility period. Nineteen patients were excluded from our study due to the absence of a cerebral venogram, unclear COVID-19 status, and history of head trauma. Out of the 115 CVT patients, 93 were in the non-COVID-CVT group and 22 were included in the COVID-CVT group (Table 1). Respiratory symptoms were observed in only 12 (54.5%) of our COVID-19 CVT patients. Specifically, eight patients had respiratory symptoms at the time of presentation, while 4 patients developed respiratory symptoms during their hospital stay.

Mean patient age was similar in both CVT groups, non-COVID and COVID, with a female predominance in the non-COVID group (52% vs. 36%). Both groups were statistically similar in terms of vascular risk factors and comorbid conditions (Table 1). However, COVID-CVT patients had a significantly longer hospital stay (14 days vs. 6 days, $p = 0.004$). Clinically, COVID-CVT patients presented with a higher frequency of headache (82% vs. 63%), seizures (64% vs. 37%, $p = 0.03$), hemiparesis (41% vs. 24%), and visual changes (36% vs. 19%) as compared to non-COVID-CVT patients. Ninety-four percentages of the patients with COVID-CVT had a headache for a duration of ≤1 week.

Brain imaging findings showed increased vasogenic edema (50% vs. 20%, $p = 0.01$) and venous infarctions (59% vs. 46%) in COVID-CVT patients while the frequency of parenchymal hemorrhages remained the same. Venogram showed a higher frequency of superior sagittal sinus (64% vs. 42%) and internal jugular vein (23% vs. 12%) involvement in the COVID-CVT cohort. Laboratory prothrombotic workup was limited and not performed in all the patients. The available results were similar in both groups except for a higher frequency of low protein S serum levels and antiphospholipid antibodies seen in the non-COVID-CVT cohort (Table 2). Antiphospholipid antibodies were checked in one-third of COVID-CVT patients and all came negative.

More than 90% of patients in both groups received therapeutic anticoagulation. Three COVID-CVT patients underwent surgical intervention; mechanical thrombectomy, intravenous thrombolysis, and ventriculoperitoneal shunt in each patient. Interestingly, decompressive hemicraniectomy was not performed in any of the COVID-CVT patients, while it was the main surgical intervention (80%; 4/5) performed in non-COVID-CVT patients. Mortality rates were higher in COVID-CVT group (18% vs. 11%) (Table 1).

Discussion

Ever since prothrombotic complications have been reported in COVID-19 patients, a wide interest has grown in the medical fraternity looking into systemic thrombotic complications [9–11]. A higher frequency and severity of arterial strokes have been reported in COVID-19 patients [12, 13], but the numbers were not the same for CVT, which was mainly restricted to isolated case reports, case series, and descriptive studies [1–7, 10]. CVT started trending when some of the COVID-19 vaccine recipients were diagnosed with this condition [14, 15].

CVT is traditionally commonly reported in young- and middle-aged females [16–18]. However, most of the previous COVID-19 CVT studies reported a male

Table 1. Patient characteristics – comparing non-COVID and COVID-CVT

Characteristic	Non-COVID-CVT (*n* = 93)	COVID-CVT (*n* = 22)	*p* value
Mean age (±SD), years	42.63 (±14.95)	45.0 (±12.03)	0.49
Mean length of hospital stay (±SD), days	5.67 (±4.39)	13.95 (±11.04)	**0.004**
Male, *n* (%)	45 (48.4)	14 (63.6)	0.24
Past history of CVT	0	1	–
Vascular comorbidities, *n* (%)			
DM	18 (19.4)	5 (22.7)	0.77
HTN	29 (31.2)	9 (40.9)	0.45
IHD	3 (3.2)	2 (9.1)	–
Malignancy	3 (3.2)	0	–
Pregnancy	7 (7.5)	0	–
Puerperium	6 (6.5)	2 (9.1)	–
Symptoms			
Headache, *n* (%)	59 (63.4)	18 (81.8)	0.13
<2 days	19 (32)	5 (28)	
2 days – 1 week	24 (41)	12 (67)	
>1 week	16 (16)	1 (5)	
Seizure, *n* (%)	34 (36.6)	14 (63.6)	0.03
1	8 (24	3 (21)	
≥2	26 (76)	11 (79)	
Generalized-onset	32 (94	11 (79)	
Focal onset	2 (2)	3 (21)	
Motor weakness, *n* (%)	22 (23.7)	9 (40.9)	0.12
Vomiting, *n* (%)	26 (28.0)	8 (36.4)	0.45
Visual changes, *n* (%)	18 (19.4)	8 (36.4)	0.10
Therapeutic anticoagulation, *n* (%)	86 (92)	20 (91)	
Choice of anticoagulant, *n* (%)			
Enoxaparin	36 (41.9)	7 (35.0)	
Warfarin	10 (11.6)	6 (30.0)	
Rivaroxaban	40 (46.5)	7 (35.0)	
Modified Rankin Score at discharge, *n* (%)			
0–2	64 (68.8)	13 (59)	0.45
3–5	19 (20)	5 (22)	
Surgical intervention, *n* (%)	5 (5.4)	3 (13.6)	
Mortality (mRs = 6), *n* (%)	10 (11)	4 (18)	

COVID, coronavirus disease 2019; CVT, cerebral venous thrombosis.

predominance [3, 4] and a relatively older age [3–5], similar to our study, except for one case series in which all CVT patients with COVID-19 were female [5]. Although the numbers, in our study, are not statistically significant, some of the reasons for these findings are that both male gender and older age are associated with worse outcomes with COVID-19 [19, 20]. A significantly longer hospital stay in our COVID-CVT patients, with relatively higher mortality and modified Rankin score (mRS) at discharge, also attests to it.

Both CVT groups, in our study, were mostly similar in terms of medical comorbid conditions and vascular risk factors, except none of the females in the COVID-CVT group were pregnant at the time of CVT diagnosis. This can be explained by differences in pathophysiology, with COVID-19 infection resulting in a pro-inflammatory state leading to thrombosis rather than hormonal changes causing a prothrombotic state [21]. On the contrary, we had a similar frequency of CVT patients in the puerperium period at the time of diagnosis in both groups, even a slightly higher percentage in the COVID-CVT group if you consider the difference in male-to-female ratios in both groups. This gives us other explanations that either our sample size is too small to have a plausible conclusion or COVID-19 pathophysiology may work in tandem with hormonal changes in creating a prothrombotic state or possibly, a combination of both. Nevertheless, we need further studies with larger sample sizes to further evaluate these findings.

Table 2. Investigations – comparing non-COVID and COVID-CVT

Characteristic	Non-COVID-CVT (*n* = 93)	COVID-CVT (*n* = 22)	*p* value
Laboratory abnormalities, *n/N* (%)			
Low protein C	7/45 (16)	2/9 (22)	–
Low protein S	11/48 (23)	0/9	–
Low antithrombin III	0/45	0/8	–
High homocysteine	30/52 (58)	4/10 (40)	0.43
Anemia	42/93 (45.2)	6/16 (37.5)	0.80
Anti-lupus Abs	2/29 (7)	2/8 (25)	–
Antiphospholipid Abs	3/30 (10)	0/7	–
Anti-nuclear Abs	6/22 (27)	2/7 (29)	–
Diagnostic imaging, *n* (%)			
MRI brain	93 (100)	19 (86.4)	
CT brain	8 (8.6)	5 (22.7)	
MRV brain	86 (93.5)	18 (81.8)	
CTV brain	6 (6.5)	4 (18.2)	
Imaging findings, *n* (%)			
Normal	14 (15.1)	4 (18.2)	0.75
Venous infarct	43 (46.2)	13 (59.1)	0.35
Hemorrhage	42 (45.2)	10 (45.5)	1.0
Edema	20 (21.5)	11 (50)	**0.01**
Subarachnoid hemorrhage	6 (6.5)	0	–
Midline shift	9 (9.7)	4 (18.2)	–
Subdural hematoma	4 (4.3)	1 (4.5)	–
Meningeal enhancement	20 (21.5)	4 (18.2)	–
Sinus involvement, *n* (%)			
Superior sagittal	39 (41.9)	14 (63.6)	0.1
Transverse	61 (65.6)	11 (50.0)	0.22
Straight	11 (11.8)	5 (22.7)	–
Sigmoid	46 (49.5)	13 (59.1)	–
Internal jugular vein	11 (11.8)	5 (22.7)	–
Cortical veins	4 (4.3)	1 (4.5)	–
Cavernous	7 (7.5)	2 (9.1)	–

COVID, coronavirus disease 2019; CVT, cerebral venous thrombosis.

Clinically, headaches and seizures were the most common symptoms in both groups. Most COVID-CVT patients (95%) had a new-onset headache of less than 1-week duration. The headache finding can be confusing, as it may occur as a part of a viral febrile illness. Seizures also occur more frequently, almost twice as common, in COVID-CVT cohort. These features signify the importance of having a low threshold for screening COVID-19 patients with new-onset headaches and seizures for CVT. The higher frequency of seizures in the COVID-CVT group could be explained by a higher incidence of venous infarcts (59%) and edema (50%) on brain imaging. The reason for worsened imaging findings is, however, unclear. Serum thrombotic workup was not performed in all of the patients and their interpretation will be misleading.

COVID-CVT was treated similarly to non-COVID-CVT, with most patients (>90%) receiving therapeutic anticoagulation. In spite of the standard treatment in both groups, COVID-CVT patients had higher mortality and a higher mRS score at the time of discharge as compared to non-COVID-CVT patients. Other studies have also reported higher mortality in this cohort of patients [3, 22, 23]. The numbers, in our study, are not statistically significant, but there is a plausible explanation for it. COVID-19 independently increases the risk for systemic complications, including death [23]. Interestingly, the Indian study reported no mortality and a better mRS score at discharge in their COVID-CVT patients compared to non-CVT patients [6]. Another surprising finding in our study was the higher mortality rate (11%) observed in our cohort of non-COVID-19 CVT patients. Our previous multicenter pre-COVID-19 study reported a combined CVT mortality rate of 3.3% [16]. Although the exact cause of this increased mortality in the non-

COVID-19 population remains unclear, delayed patient presentation to hospitals during the COVID-19 pandemic period (our study period) may provide a plausible explanation. Individuals may have avoided hospital visits due to the risk of contracting COVID-19, which could have led to delayed diagnoses and treatment.

Our study has several limitations. We had a small sample size, especially of COVID-CVT patients, making it difficult to draw significant comparisons between both groups. Our study was also retrospective in nature, consisting only of the inpatient population, and conducted in a single tertiary care center. Since this was a single-point retrospective analysis of existing patient data, causality cannot be reliably established. Therefore, there is a need to conduct large-scale studies to establish more meaningful comparisons between these two groups.

Statement of Ethics

Study was approved by Ethics Review Committee of Aga Khan University (2020-5204-11458). The need for informed consent was waived by Ethics Review Committee of Aga Khan University.

Conflict of Interest Statement

Authors have no conflict of interest to disclose

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Author Contributions

Sajid Hameed and Mohammad Wasay: concept, data collection, data analysis, manuscript writing, and manuscript review. Anwar Hamza, Bushra Taimuri, and Maria Khan: data analysis, manuscript writing, and manuscript review. Man Mohan Mehndiratta: data analysis and manuscript review.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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