

Cerebral Venous Thrombosis Associated with COVID-19 Infection: An Observational, Multicenter Study

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Keywords

COVID-19 · Cerebral venous thrombosis · Hemorrhage · Coagulopathy · Stroke

Abstract

Background and Purpose: Coronavirus disease 2019 (COVID-19) has an increased propensity for systemic hypercoagulability and thromboembolism. An association with cerebrovascular diseases, especially cerebral venous thrombosis (CVT), has been reported among these patients. The objective of the present study was to identify risk factors for CVT as well as its presentation and outcome in COVID-19 patients. **Methods:** This is a multicenter and multinational observational study. Ten centers in 4 countries (Pakistan, Egypt, Singapore, and the United Arab Emirates) participated in this study. The study included patients (aged >18 years) with symptomatic CVT and recent COVID-19 infection. **Results:** Twenty patients (70% men) were included. Their mean age was 42.4 years, with a male-to-female ratio of 2.3:1. Headache (85%) and seizures (65%) were the common presenting

symptoms, with a mean admission Glasgow Coma Scale (GCS) score of 13. CVT was the presenting feature in 13 cases (65%), while 7 patients (35%) developed CVT while being treated for COVID-19 infection. Respiratory symptoms were absent in 45% of the patients. The most common imaging finding was infarction (65%), followed by hemorrhage (20%). The superior sagittal sinus (65%) was the most common site of thrombosis. Acute inflammatory markers were raised, including elevated serum D-dimer (87.5%), erythrocyte sedimentation rate (69%), and C-reactive protein (47%) levels. Homocysteine was elevated in half of the tested cases. The mortality rate was 20% (4 patients). A good functional outcome was seen in the surviving patients, with a mean modified Rankin Scale score at discharge of 1.3. Nine patients (45%) had a modified Rankin Scale score of 0–1 at discharge. **Conclusion:** COVID-19-related CVT is more common among males at older ages when compared to previously reported non-COVID-19-related CVT cases. CVT should be suspected in COVID-19 patients presenting with headache or seizures. Mortality is high, but functional neurological outcome is good among survivors.

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Introduction

Coronavirus disease 2019 (COVID-19) is a novel infection caused by the SARS-CoV-2 coronavirus, resulting in severe acute respiratory syndrome (SARS). An increased propensity for systemic hypercoagulability and thromboembolism has been reported among COVID-19 patients [1–3]. In one study, thrombotic complications were reported in approximately one-third of the critically ill COVID-19 patients [1]. An increase in cerebrovascular diseases (1–6%) has also been reported among these patients [4]. Published data on cerebral venous thrombosis (CVT) among COVID-19 patients are limited. Hughes et al. [5] published the first case of CVT in a COVID-19 patient in April 2020. To the best of our knowledge, only 12 CVT cases among COVID-19 patients have been reported in the literature [6]. All these cases are presented in single-center case reports. The purpose of this study was to identify the risk factors for CVT as well as its presentation and outcome in COVID-19 patients in a multinational, multicenter setting using a prespecified data collection tool.

Subjects and Methods

We conducted a multicenter observational study. Ten centers in 4 countries (Pakistan, Egypt, Singapore, and the United Arab Emirates) participated in the study. All 10 centers are tertiary care hospitals with full-time neurologists and availability of diagnostic modalities for the diagnosis of CVT as well as COVID-19. Data were collected on a prespecified questionnaire. They were collected retrospectively from COVID-19 registries and hospital medical records. All patients fulfilling the inclusion criteria were included. One male patient with recent head trauma with COVID-19 and CVT was excluded. Patients aged 18 years or above with recent COVID-19 infection, confirmed either by reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab or serum antibody testing for COVID-19, were included. Diagnosis of CVT was confirmed by at least one of the following imaging studies according to the established criteria: magnetic resonance (MR) imaging, MR venography (MRV), computed tomography (CT), CT venography, or cerebral venography. Patients with recent trauma and patients already receiving anticoagulation were excluded. The data included risk factors, clinical features, laboratory findings, imaging findings, COVID-19-related information, and data on management and outcome for all patients enrolled in the study. The patients were identified through the medical record system of the hospitals and COVID-19 registries at the various centers. Data are presented as frequencies and correlations.

Results

A total of 20 cases were included (Table 1) from 4 countries (13 from Pakistan, 4 from Egypt, 2 from Singapore, and 1 from the United Arab Emirates). Eighteen cases (90%) tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab, while 2 cases (10%) tested positive for COVID-19 antibodies. Out of 20 subjects, 14 were male (70%). The average age was 42.4 years. In 19 cases (95%), the diagnosis of CVT was confirmed by MRV and/or CT venography, while 1 patient had a noncontrast CT scan suggestive of superior sagittal sinus thrombosis.

Clinical Features, Risk Factors, and Comorbid Conditions

Headache (85%, $n = 17$) and seizures (65%, $n = 13$) were the most common neurological features. Headache was of 3–7 days in duration in 76% of the cases. Seizures were of generalized onset in 10 cases (77%) and focal onset in 3 cases (23%). The mean Glasgow Coma Scale (GCS) score on admission was 13. Cigarette-smoking (45%, $n = 9$) and hypertension (35%, $n = 7$) were the most common vascular risk factors present. One female was on oral contraceptives despite a previous history of CVT. One female had a history of deep venous thrombosis, and 1 male had polycythemia. Four cases were dehydrated (20%) on presentation.

Relationship to COVID-19 Infection

CVT was the presenting feature in 13 (65%) of cases, whereas 7 (35%) developed CVT while being treated for COVID-19 infection. Two patients with positive COVID-19 antibodies likely presented with late-stage COVID-19. Nine cases (45%) did not have respiratory symptoms at the time of diagnosis of CVT. In 5 patients (25%), CVT was the sole presentation of COVID-19 (absence of fever and respiratory symptoms).

Laboratory Workup and Imaging Findings

Important laboratory findings included elevated levels of serum D-dimer (87.5%), erythrocyte sedimentation rate (69%), and leukocytosis (72%). Homocysteine was elevated in 50% of the tested cases. Two out of 9 patients had positive lupus anticoagulant (LA). The most common imaging finding was infarction (65%, $n = 13$), more than one-third of which were hemorrhagic infarcts (38%, $n = 5$), followed by hemorrhage only in 4 patients (20%). The superior sagittal sinus was the most common site of thrombosis (65%, $n = 13$) using all modalities.

Table 1. Patients with COVID-19 and CVT

Pa-tient No.	Country	A/G, years	PMH	Neurological features	GCS score*	Respiratory symptoms/ COVID-19 testing	Brain imaging findings (involved vessels)	CVT risk factors	Treatment	Outcome/ mRS score
1	Pakistan	34/F	-	Headache, seizures, hemiparesis	15	PCR Pos. URTI	Infarction (SSS)	-	Rivaroxaban	1
2	Pakistan	36/M	HTN, CS	Headache, seizures, fever	11	PCR Neg. Antibodies Pos.	Bifrontal hemorrhage (SSS + TS + sigmoid sinus)	Dehydration + homocysteinemia	Rivaroxaban	2
3	Pakistan	52/M	-	Fever, altered mentation	12	PCR Pos. URTI	IJV + sigmoid sinus thrombus	-	LMWH	2
4	Pakistan	80/M	-	Headache, hemi-numbness	15	PCR Pos.	Hemorrhage (SSS)	-	Rivaroxaban	1
5	Pakistan	45/M	DM, CS	Headache, vision loss, hemiparesis	8	PCR Pos. URTI	Infarction + edema (cavernous sinus)	Dehydration	UFH	Death
6	Pakistan	44/M	CS	Headache, seizure, hemiparesis	15	PCR Pos.	Infarction (TS + sigmoid sinus ext. into IJV)	-	LMWH rivaroxaban	1
7	Pakistan	29/M	-	Headache, seizures, hemiparesis	15	PCR Pos.	Hemorrhagic infarction (SSS + TS + sigmoid sinus)	Homocysteinemia + low protein C	LMWH + thrombectomy	3
8	Pakistan	41/F	HTN	Headache, seizures, altered mentation	14	PCR Pos.	Infarction (SSS + TS + sigmoid sinus + straight sinus)	Dehydration	LMWH + warfarin	2
9	Pakistan	54/M	DM, HTN, CS	Headache, vision loss, hemiparesis, seizures	N/A	PCR Neg. Antibodies Pos. Pneumonia	Hemorrhagic infarction (SSS + straight sinus + sigmoid sinus)	-	No anticoagulation	2
10	Pakistan	54/F	DM, HTN, CS	Headache, diplopia, hemiparesis, seizures	N/A	PCR Pos. Pneumonia	Infarction	History of deep vein thrombosis	No anticoagulation	4
11	Pakistan	36/F	DM, HTN, CAD	Headache, hemiparesis, seizures	N/A	PCR Pos. Pneumonia	Hemorrhagic infarction (SSS + sigmoid sinus)	-	UFH	1
12	Pakistan	32/M	CS	Headache	15	PCR Pos. URTI	(SSS + TS + sigmoid sinus + ext. into IJV)	-	LMWH rivaroxaban	0
13	Pakistan	43/F	HTN	Headache, seizures, papilledema	14	PCR Pos.	Infarction (SSS + TS + straight sinus)	-	LMWH + warfarin	2
14	Egypt	36/F	Obesity, gestational HTN	Headache, seizures	15	PCR Pos.	Infarction + edema (SSS + TS)	Postpartum homocysteinemia	LMWH + warfarin	1
15	Egypt	33/F	Migraine, CS	Headache, seizures, hemiparesis	8	PCR Pos. Pneumonia	Infarction (TS + straight sinus + sigmoid + cavernous sinus)	CVST + oral contraceptive pills + antiphospholipid Abs	LMWH + IV thrombolysis	Death
16	Egypt	42/M	CS	Headache, seizures, altered mentation	10	PCR Pos. Pneumonia	Infarction (SSS + TS + straight sinus)	Homocysteinemia	LMWH	Death
17	Egypt	43/M	CS	Headache, blurred vision	13	PCR Pos. Pneumonia	Cerebral edema (SSS)	-	UFH + warfarin + VP shunt	1

Table 1 (continued)

Patient No.	Country	A/G, years	PMH	Neurological features	GCS score*	Respiratory symptoms/ COVID-19 testing	Brain imaging findings (involved vessels)	CVT risk factors	Treatment	Outcome/ mRS score
18	Singapore	38/M	CS	Generalized-onset seizures	10	PCR Pos.	Hemorrhagic infarction + edema (TS + sigmoid sinus)	Homocysteinemia + low protein C + antiphospholipid Abs	UFH + warfarin + craniectomy	Death
19	Singapore	35/M	-	Headache	15	PCR Pos. Pneumonia	(TST + sigmoid sinus)	-	Dabigatran	1
20	UAE	41/M	HTN	Seizures	14	PCR Pos.	Hemorrhage (SSS + cortical vein)	PCT (polycythemia)	LMWH + warfarin phlebotomies	0

Abs, antibodies; A/g, age and gender; CS, cigarette-smoking; CVST, cerebral venous sinus thrombosis; CVT, cerebral venous thrombosis; DM, diabetes mellitus; EVD, extraventricular drain; F, female; Inc., increased; IV, internal jugular vein; HTN, hypertension; LMWH, low-molecular-weight heparin; Lt., left; M, male; mRS, modified Rankin Scale; N/A, not available; N/V, nausea and vomiting; Neg., negative; NPS, nasopharyngeal swab; PCT, polycythemia; PMH, past medical history; Pos., positive; Rt., right; SSS, superior sagittal sinus; TS, transverse sinus; UAE, United Arab Emirates; UFH, unfractionated heparin; URTI, upper respiratory tract infection; VP shunt, ventriculoperitoneal shunt.

Management and Outcome

Eighteen cases (90%) received systemic anticoagulation treatment, with the majority of the patients receiving low-molecular-weight heparin (56%, *n* = 10) and unfractionated heparin (22%, *n* = 4) for initial anticoagulation. Besides anticoagulation, thrombectomy, intravenous thrombolysis, ventriculoperitoneal shunt, and decompressive craniectomy with extraventricular drain placement were performed on 1 patient each.

Fifteen cases (75%) were discharged home with an improving condition, 4 cases (20%) died, and 1 case (5%) was referred to another hospital for rehabilitation. All 4 patients who died had a low GCS score (8–10) at admission. The discharged cases had an average modified Rankin Scale score of 1.3. Patients with good functional outcome had no or mild respiratory symptoms, a high GCS score (13–15) at admission, and/or a normal brain parenchyma on imaging.

Discussion

This is the first and the largest multicenter and multinational study of CVT in COVID-19 patients. This patient population differs in many aspects from previously reported non-COVID-19 CVT patients, where CVT is more common in the third decade of life with a female predominance [7–9]. In this study, males were twice as frequently affected, with an average age of 42.4 years. Although the incidence of CVT increases during the puerperal period and is associated with oral contraceptive pill (OCP) use (11–54%) [7–11], in our study only 1 patient was in the puerperal period (3 days after cesarean section) and 1 patient had a history of OCP use.

A hypercoagulable state is an important and well-known risk factor for CVT [10–14]. In a study among critically ill COVID-19 patients (*n* = 184), 31% of the patients developed thrombotic complications, with pulmonary embolism topping the list [1]. Similarly, another study reported a high frequency of venous thromboembolism (21%) among COVID-19 patients [2]. An increased LA positivity is reported in acute COVID-19 infections [3, 12, 13]. These LA antibodies are presumed to increase the risk of thromboembolism but are transiently elevated in the acute viral setting [14]. A prolonged activated partial thromboplastin time in the presence of LA does not increase the bleeding risk, and these patients may receive anticoagulation if clinically indicated [15]. In our study, 9 cases (45%) also did not have respiratory symptoms. Tan et al. [12] reported an absence of respira-

tory symptoms in 24% of their COVID-19 patients with acute ischemic stroke.

SARS-CoV-2, responsible for COVID-19 infection, is well known to bind angiotensin-converting enzyme (ACE) 2 receptors, which are variably present in the arterial and venous vascular endothelium. Autopsy studies have revealed that ACE2 receptors are more abundant in the arterial endothelium than in the venular endothelium [16]. This expression of ACE receptors probably explains the high frequency of arterial stroke. COVID-19 not only causes direct vascular damage but may also create an intense inflammatory reaction affecting hemostasis and the coagulation cascade. COVID-19-associated arterial stroke predominantly affects younger males with vascular risk factors and mostly presents as large vessel stroke [17]. These findings may suggest a common pathway for both COVID-19-associated CVT and arterial stroke.

The main limitations of our study are selection bias, the absence of a control sample, the absence of prothrombotic workup, limited neurological examination, and the inability to examine the influence of confounding variables on outcomes. The current number of CVT cases is probably an underestimation. COVID-19 testing may be included as standard workup among all CVT patients, including those who have no throat or respiratory symptoms. All COVID-19-positive patients with headache and neurological symptoms should be evaluated for CVT. Early diagnosis by MRI and MRV and anticoagulation for high-risk populations (with a history of venous thromboembolism, a postpartum state, or use of OCPs) may lead to improved outcomes.

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Statement of Ethics

The study protocol was approved by the Ethics Review Committees of Aga Khan University, Karachi (Ref. 2020-5204-11458), and the participating centers. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All participants or their guardians have given written informed consent.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

S.H.: data acquisition, data analysis, manuscript writing, and manuscript review. M.W.: concept, collaboration, data acquisition, data analysis, manuscript writing, and manuscript review. B.A.S., O.M., F.A., T.T., R.F., N.S., H.H., W.A., A.I., and M.K.: data acquisition, manuscript writing, and manuscript review.

Data Availability Statement

All research data are available and can be accessed via the corresponding author.

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