Cerebral Venous Sinus Thrombosis Associated With Coronavirus Disease 2019

Case Report and Review of the Literature

Kessarin Panichpisal, MD, Ilana Ruff, MD,* Maharaj Singh, PhD,†‡ Massihullah Hamidi, MD,* Pedro D. Salinas, MD,§ Kyle Swanson, MD,* Stephen Medlin, DO,‖ Sudeepta Dandapat, MD,* Payton Tepp, NP,* Genevieve Kuchinsky, NP,* Amy Pesch, NP,* and Thomas Wolfe, MD**

Introduction: Coronavirus disease 2019 (COVID-19) is associated with significant risk of acute thrombosis. We present a case report of a patient with cerebral venous sinus thrombosis (CVST) associated with COVID-19 and performed a literature review of CVST associated with COVID-19 cases.

Case Report: A 38-year-old woman was admitted with severe headache and acute altered mental status a week after confirmed diagnosis of COVID-19. Magnetic resonance imaging brain showed diffuse venous sinus thrombosis involving the superficial and deep veins, and diffuse edema of bilateral thalami, basal ganglia and hippocampi because of venous infarction. Her neurological exam improved with anticoagulation (AC) and was subsequently discharged home. We identified 43 patients presenting with CVST associated with COVID-19 infection. 56% were male with mean age of 51.8 ± 18.2 years old. The mean time of CVST diagnosis was 15.6 ± 23.7 days after onset of COVID-19 symptoms. Most patients (87%) had thrombosis of multiple dural sinuses and parenchymal changes (79%). Almost 40% had deep cerebral venous system thrombosis. Laboratory findings revealed elevated mean D-dimer level (7.14/mL ± 12.23 mg/L) and mean fibrinogen level (4.71 ± 1.93 g/L). Less than half of patients had prior thrombotic risk factors. Seventeen patients (52%) had good outcomes (mRS < = 2). The mortality rate was 39% (13 patients).

Conclusion: CVST should be in the differential diagnosis when patients present with acute neurological symptoms in this COVID pandemic. The mortality rate of CVST associated with COVID-19 can be very high, therefore, early diagnosis and prompt treatment are crucial to the outcomes of these patients.

Key Words: cerebral venous sinus thrombosis and COVID-19, dural sinus, thrombosis, COVID-19

(*The Neurologist* 2022;27:253–262)

Since Wuhan, China reported the first case of coronavirus disease 2019 (COVID-19) in December 2019, this pandemic has affected 105 million people and has caused over 2.3 million deaths worldwide (as of February 5, 2021).[1]

From the onset of the pandemic, thromboembolic complications of COVID-19 have been well recognized and not limited to patients with severe infection. A systemic review and meta-analysis of risk of venous thromboembolism in COVID-19 patients demonstrated that VTE occurs in 22.7% in ICU patients and 7.9% of non-ICU hospitalized patients.[2] Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a neurotropic virus, and one of the cardinal symptoms of the disease includes loss of smell and taste disturbance. The reported incidence of neurological manifestations from the largest hospital-based study was 57.4%. Nonspecific symptoms like myalgias, headache, dizziness, anosmia, and dysguesia are most likely to be reported in the early stage of infection, and disorder of consciousness is the most common symptom in severe and advanced COVID-19 stages.[3] The incidence of reported acute cerebrovascular disease in COVID-19 patients ranges from 0.5% to -5.9%[4] There have been several case reports of cerebral venous sinus thrombosis (CVST) associated with COVID-19, with an incidence of 0.3% to 0.5% in the reported literature.[5–32] This may underestimate the incidence of acute ischemic vascular events in these patients, given the high reports of neurological symptoms and the challenges of imaging patients with COVID-19.

Here we report the case of a young woman who presented to our hospital with CVST during a COVID-19 infection and provide a literature review of all cases reported in English literature.

CASE REPORT

A 38-year-old woman, with a history of Crohn disease on immunosuppressive therapy, history of Mycobacterium avium-intracellulare infection, migraine, anxiety, vitamin B12 and vitamin D deficiency and history of pulmonary embolism and DVT (not on AC) developed cough, fever and malaise and tested positive for COVID-19 on September 27, 2020. One weeks after confirmed COVID-19 diagnosis and fully recovered from her respiratory symptoms, she developed a bifrontal headache and went to urgent care clinic and was advised to take acetaminophen.

On October 8, 2020, she was found unresponsive and covered in feces on her front porch by her neighbors. She was brought to the emergency department. Her vital signs were significant for temperature 97.6 F (36.4°C), blood pressure 119/61, pulse 89/minute, and oxygen saturation 96%. She was alert, and withdrawn, being able to respond appropriately to yes/no questions by squeezing her hands and was noted to have no respiratory distress or other focal neurological findings on examination. Her initial computed tomography (CT) brain showed evidence of bilateral thalamic and basal ganglia hypodensities and hyperdense signal in the straight sinus, vein of Galen and internal cerebral veins (Fig. 1). Her chest X-ray was normal. SARS-CoV-2 by qualitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) assay was positive.

From the *Aurora Neurosciences Innovative Institute; ‖Aurora Cancer Care, Aurora St. Luke's Medical Center; §Aurora Critical Care Services, Aurora Sinai/Aurora St. Luke's Medical Centers, University of Wisconsin School of Medicine and Public Health; †School of Dentistry, Marquette University; and ‡Aurora Research Institute, Milwaukee, WI.
The authors declare no conflict of interest.
Correspondence to: Thomas Wolfe, MD, 2801 W Kinnickinnic River Pkwy #680, Milwaukee, WI 53215. E-mail: thomas.wolfe@aah.org.

ISSN: 2331-2637/22/2705-0253
DOI: 10.1097/NRL.0000000000000390

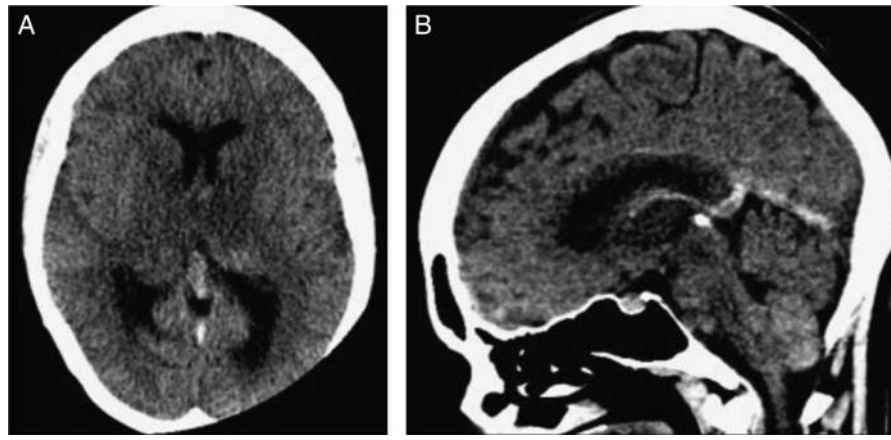

FIGURE 1. Axial (A) and Sagittal (B) noncontrast computed tomography of brain showing bilateral thalamic and basal ganglia hypodensities and hyperdense straight sinus, vein of Galen and internal cerebral veins.

Lumbar puncture was performed and showed cerebrospinal fluid (CSF) pleocytosis and high protein. CSF venereal disease research laboratory, cryptococcal antigen, rapid meningitis/encephalitis panels and culture were unremarkable. Magnetic resonance imaging (MRI) brain showed restricted diffusion in the bilateral caudate, thalamus, external capsule, and obstructive hydrocephalus from edema related mass effect, with sinus venous thrombosis in the deep venous system extending proximally from the right basal vein of Rosenthal and internal cerebral veins, to the vein of Galen and straight sinus, torcula, right transverse/sigmoid, and internal jugular vein (Fig. 2).

She was transferred to our tertiary hospital. On arrival, her examination was notable for being drowsy and inattentive, she was able track and fixate on the examiner and mouth words, but she was hypophonic. She had left adduction palsy with right nasolabial fold flattening and bilateral drift in her arms, bilateral arm dysmetria, and was able to lift her legs against gravity. Her mental status fluctuated. Because of hydrocephalus, a right external ventricular drain (EVD) was placed. The CSF pressure was <10 cm H_2O. Heparin infusion was started (without initial bolus) after EVD placement, and her mental status improved. By the next morning, she was alert, attentive, vocalizing, stating her name, and location, following commands. She was moving all her extremities antigravity and purposefully and had mild right nasolabial flattening. Postoperative CT head showed moderate improving hydrocephalus. She ultimately was transitioned to enoxaparin as it was difficult to get her partial thromboplastin time (PTT) therapeutic; hematology felt that elevated FVIII (341%) and fibrinogen (4.82 g/L) may be contributing to heparin resistance. Her hypercoagulable workup was unremarkable (Table 1). On October 12, 2020, she developed emesis and headache after clamping of her drain, she was taken for head CT and MRI brain showed improvement in her venous infarcts with stable deep cerebral vein and torcula/R sigmoid/transverse/IJ thrombosis. She was found to have thin subdural hematomas, so MRI thoracic and lumbar spine were performed, revealing lumbar epidural fluid consistent with CSF leak from the lumbar puncture site. She had a blood patch placed on October 15, 2020 and her EVD was removed on October 17, 2020 after successful wean. She was discharged on October 22, 2020 with enoxaparin bridge to warfarin with a normal neurological examination.

Follow-up CT brain imaging (November 2, 2020) demonstrated no evidence of hydrocephalus and resolution of the hypodensities in her deep nuclei and subdural fluid collections (Fig. 3). Her neurological examination was normal at her follow-up outpatient appointment in December 2020.

METHODS

We reviewed the worldwide English-language medical literature in the MEDLINE database, using the MESH terms "COVID-19" and "Cerebral venous thrombosis," "SAR-CoV-2," and "Cerebral venous thrombosis," "Viral infection," and "Cerebral venous thrombosis" since the onset of current COVID-19 epidemic, December 2019 to February 4, 2020. We included all case reports of adults age 15 years old or elder and excluded cases that did not provide individual patient data and duplicated case reports that were published in separated case series.[5–32]

Statistical Analysis

From all individual case reports the variables were described using descriptive statistics. For example, all categorical variables were expressed as frequency and percentage, whereas all numeric continuous variables were described as mean and SD. The variables were compared across 2 types of outcomes using χ^2 and/or the Fisher exact test for categorical variables and t test for continuous numeric variables. For all statistical test an alpha of 0.05 was used as level of significance. All statistical analysis was done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

We identified a total of 43 cases (including our case) of CVST associated with COVID-19 (Table 2).[5–32] COVID-19 infection was diagnosed through nasopharyngeal swabs for SARS-CoV-2 PCR in 95% (35/37 patients). Two patients had negative SARS-CoV-2 PCR tests; 1 patient was diagnosed based on clinical and radiographic feature, and another 1 had positive SARS-CoV-2 antibodies. Thirty-eight patients (93%) had classic COVID-19 symptoms with or without abnormal chest imaging.

The mean age was 51.8 ± 18.2 years (range: 17 to 81), 24 patients (56%) were male. Table 3 summarizes clinical features, risk factors, and radiographic findings. The mean time of CVST diagnosis was 15.6 ± 23.7 days after onset of COVID-19 symptoms (range −1 d to 120 d). Five patients (15%) had CVST as their first clinical manifestation of COVID-19 disease and 5 patients (15%) developed CVST during recovery phase of disease (negative COVID-19 test at the time of presentation with CVST). Twenty-eight patients (85%) presented within 1 week after developing symptoms and 22 patients (67%) presented within 24 hours. The most common presentations were altered mental status (56%) and headache (49%) followed by focal neurological deficit (41%) and seizure (24%). Fourteen patients (44%) had identified thrombotic risk factors, the common risk factors included obesity, hematological disease,

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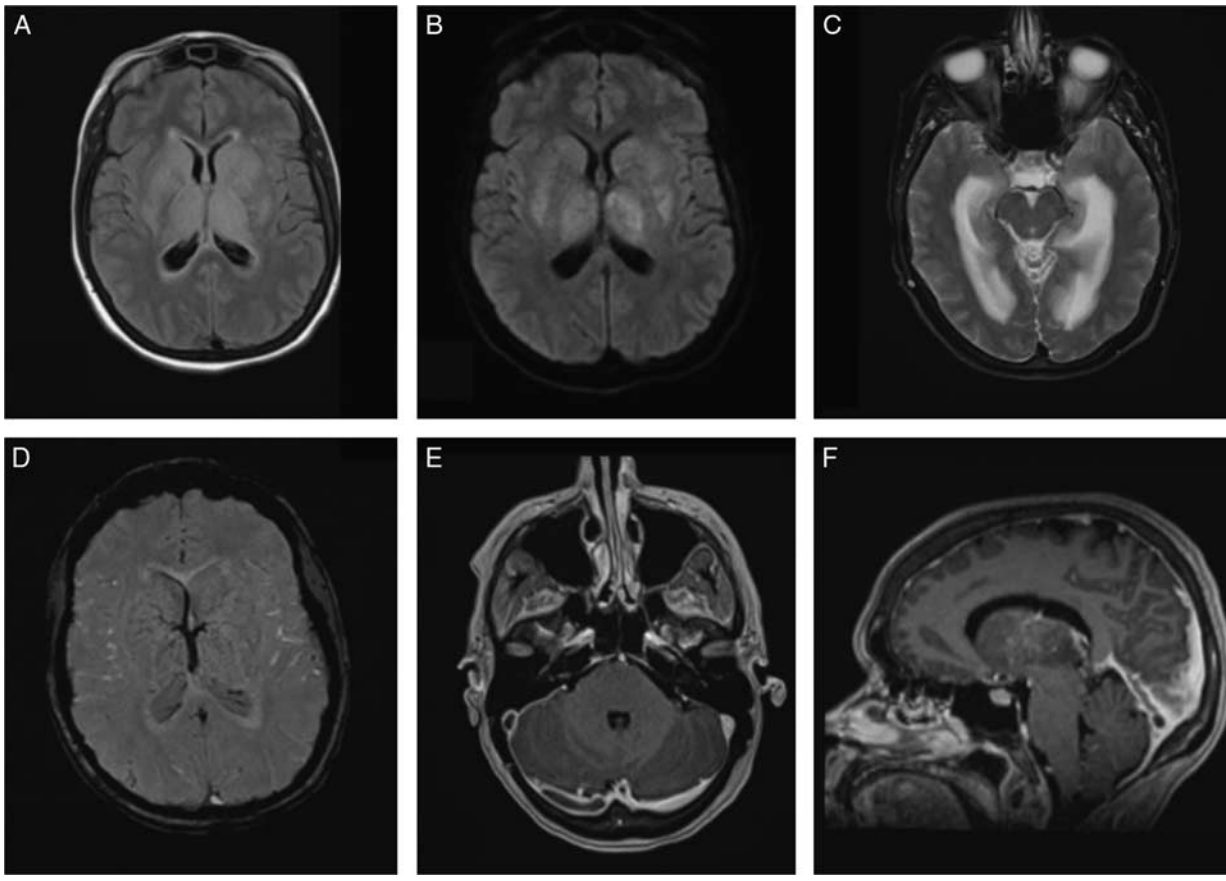

FIGURE 2. (A) Axial T2 FLAIR magnetic resonance imaging showing edema in bilateral thalami and basal ganglia (likely from venous congestion) and bilateral periventricular white matter (likely from hydrocephalus). (B) Axial DWI showing ischemia related to venous congestion in bilateral thalami and basal ganglia. (C) Axial T2 fat saturated showing hydrocephalus and associated transependymal cerebrospinal fluid flow. (D) Axial SWI showing thrombus in internal cerebral veins and their branches. (E) Axial 3D T1 postcontrast showing right transverse/sigmoid thrombus. (F) Sagittal 3D T1 postcontrast showing straight sinus/vein of Galen thrombus. DWI indicates diffusion weighted image; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility wighted image.

oral contraceptive use, and immobilization, and 1 patient had pulmonary embolism and superior vena cava thrombus. Two had concurrent large vessel occlusion arterial strokes in addition to CVST. One patient had embolic stroke prior CVST onset.

Laboratory Findings

D-dimer levels were elevated in 96% of cases with mean of 7.14 ± 12.23 mg/L. Fibrinogen level were elevated in 50% of cases with mean fibrinogen levels was 4.71 ± 1.93 g/L. Nineteen patients had hypercoagulable test done, 12 (63%) were unremarkable. Three patients had positive lupus anticoagulant and 3 had positive anti-cardiolipin antibodies identified during the evaluation of new CVST (2 of which had transient elevation). Three patients had elevated factor VIII levels. One had low protein C level. One patient had DIC.

Lumbar puncture was performed in 5 patients, mean CSF white blood cell counts was 36.8 ± 34.4 cells/μL and mean protein was 477 ± 420.26 mg/dL.

Radiologic Findings

Thirty-three patients had multiple sinuses involved. Twenty-three patients (61%) presented with sinus thrombosis of the superficial veins, 5 patients (13%) with deep CVST, and 10 patients (26%) with both. Twenty-four patients (62%) had hemorrhagic conversion, and 13 (33%) patients with venous infarcts.

Treatment

Most patients [36 cases (92%)] received AC initially; 26 received low molecular weighted heparin (LMWH), 6 received unfractionated heparin (UFH), 2 received dabigatran, and 3 of the reports reported AC without specifying the medication used in initial treatment. Three patients (13%) received supportive care without AC or intervention. Four patients did not have data reported about if AC was administered; 3 of these were noted to have cerebral hemorrhage, while the other did not specify. One (4%) patient had venous mechanical thrombectomy and local thrombolysis. Three patients (8%) had EVD and 4 patients (10%) had decompressive craniotomy or hematoma evacuation. Fifteen patients had discharge AC information available, 3 went home with warfarin, 3 dabigatran, 2 rivaroxaban, 2 edoxaban, 2 LMWH, 1 apixaban, and 1 unspecified direct oral AC.

Outcomes

Outcome data were available in 33 patients, 17 patients (52%) had good outcomes (mRS ≤ 2) at discharge. The mortality rate was 39% (13 patients) in which 2 patients died from respiratory failure and 2 patients also had massive AIS and the rest (9 patients) died from massive cerebral edema from CVST. Table 4 shows the comparison of variables between patients with good outcome and poor outcome and comparing mortality outcome. Patients with poor outcome or death significantly

TABLE 1. Summary of Laboratory Findings

	Outside Hospital	Our Hospital
White cell count (per mm^3)	**18,600**	**9700**
Total neutrophils (per mm^3)	**16,900**	**8730**
Total lymphocytes (per mm^3)	800	776
Total monocytes (per mm^3)	600	97
Hemoglobin level (g/dL)	8.5	7.3
Platelet count (per mm^3)	**542,000**	**398,000**
Activated partial thromboplastin time (s)	25	26
Prothrombin time (s)	10.9	
INR	1.0	
D-dimer level (mg/L)		**2.27**
Fibrinogen level (g/L)		**482**
Ferritin level (ng/mL)		25
Antithrombin III (%)		80
High-sensitivity CRP (mg/dL)		**2.5**
ESR (mm/h)		**65**
Plasminogen activity (%)		105
Factor VIII assay (%)		**341**
Beta2 glycoprotein (IgG, IgM, and IgA)		< 20
Cardiolipin antibodies (IgG, IgM, and IgA)		< 20
Lupus anticoagulant		Negative
Prothrombin genotype		Not detected
Activated protein C resistance		Normal ratio
JAK2 gene, V617F mutation		Not detected
Albumin (g/dL)	2.3	2
ALT (IU/L)	19	12
CSF studies		
Red blood cells (per mm^3)	**393***	
White blood cells (per mm^3)	**100**	
Glucose (mg/dL)	45	
Protein (mg/dL)	**112**	

Bold represents values outside of normal range.
*Absent xanthochromia.
ALT indicates alanine aminotransferase; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; INR, international normalized ratio.

presented with altered mental status, severe/critical COVID-19 infection, and vasogenic edema on cranial imaging. Patients with good outcome or survival presented with headache significantly more than patients with bad outcome or death. Patients with poor outcome had deep cerebral venous system involvement significantly more than patients with good outcome. Vice versa, patients with good outcome had superficial venous system involvement to a significantly higher extent than patients with poor outcome.

DISCUSSION

CVST is a rare disease, with overall incidence in the population up to 15.7 per million per year.[34] This can be a challenging diagnosis, as it presents with a nonspecific headache, and may or may not have focal neurological findings. Up to one-third of CT brain can be normal in CVST.[34] In a patient with acute encephalopathy, lumbar puncture is often performed after initial negative CT brain, however, abnormal cell counts, and protein can be observed in CSF findings of patients with CVST as well.

The mean duration of CVST from onset of COVID-19 in this review was 15.6 ± 23.7 days. Approximately one-third of the patients had CVST before or during recovery phase from COVID-19, while 15% of patients presented with CVST as the first sign of COVID-19 infection, at the beginning of their course. Consistent with our findings, CVST can develop weeks to months after initial diagnosis of COVID-19.[29] As demonstrated in this review, CVST can also occur with any COVID-19 severity.[33]

Several key differences were found in patients who presented with COVID-19 and CVST, compared with prior reports of isolated CVST. Unlike patients with CVST before the pandemic, COVID-19 CVST patients were more frequently male (58%), older (mean age was 51.8 in comparison to mean age 39.1 for CVST (16 to 86 years old) and more likely to die (mortality rate 39% in comparison to 4%).[34,35] Mortality rate for COVID-19 CVST mirrors that of acute ischemic stroke associated with COVID-19 (38%), raising the possibility of an independent effect of the infection.[34,36] We found that nonsurvival from CVST was associated with severe/critical COVID-19 infection, and that more vasogenic edema related to the CVST was present. Possible explanations for this unusually high mortality of COVID-19 CVST may relate to a direct role the virus has to influence thrombosis, how the virus affects multiple organ systems, excessive immune activation and cytokine storm contributing to hemodynamic derangements, delayed diagnosis in ventilated patients or from compromised oxygenation status in this group, or more deep venous system involvement, though our review is not able to confirm these

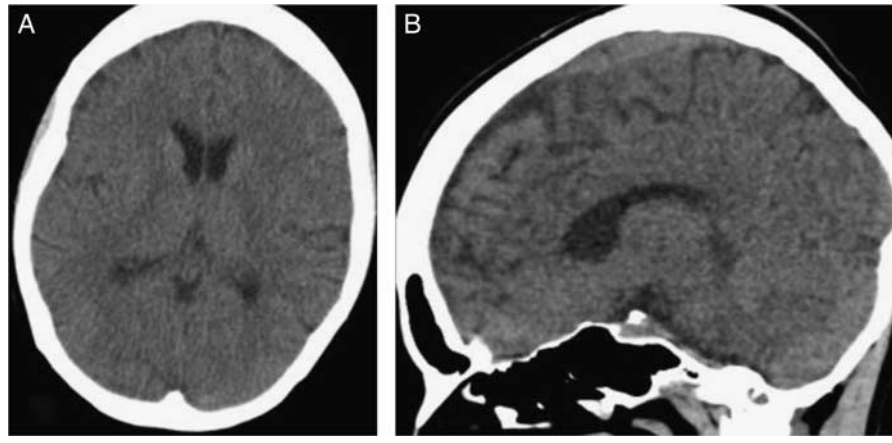

FIGURE 3. Axial (A) and Sagittal (B) noncontrast computed tomography of brain 4 weeks after presentation showing normalization of the bilateral thalamic and basal ganglia edema and resolution of the hyperdense dural venous sinus thrombosis.

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TABLE 2. Summary of All Reported Cases of CSVT Associated With COVID-19

References	Age/ Sex	Presentation	Onset */COVID-19 status†	Thrombotic Risk Factors/ Medical Problems	Sinus/Vein Involvement	Brain Lesions	D-Dimer (mg/L)	Fibrinogen (g/L)	Initial Treatment	mRS at d/c
5	33/F	Headache, seizure	−1 d Mild	Obesity, estrogen containing OCP	Left parietal cortical vein	Left parietal vasogenic edema	**0.90**	**4.2**	Dabigatran	0
6	63/ M	FND, seizure	9 d Mild	DM, asthma	Right TS, SS, and SSS	Bilateral cortical venous infarcts, cortical ICH	**4.77**	**5.68**	LMWH	3
7	38/ M	Headache, AMS	3 d Critical	Dehydration Autism spectrum disorder	Right ICV, STS, right TS, torcula, cortical veins	Significant cerebral edema	**> 55**	1.21	LMWH Endovascular Rx	6‡
7	41/F	FND, AMS	NA Critical	Estrogen containing OCP	Bilateral ICVs, VOG, distal STS	Left basal ganglia, thalamus, temporal lobe venous infarction with hemorrhagic transformation, IVH, obstructive hydrocephalus	**2.03**	NA	UFH EVD	6
8	72/ M	FND, AMS, refractory status epilepticus	A few days Mild	None	Bilateral ICVs, thalamostriate veins, bilateral BVR, VOG	Hemorrhagic venous infarction at right thalamus, basal ganglia, internal capsule, corpus callosum, and the deep white matter later developed vasogenic edema of the right cerebral peduncle and the pons, IVH, dilated medullary veins.	NA	NA	Anticoagulant (NS)	6
9	72/F	FND, AMS	60 d§ Mild	Polycythemia Vera Ischemic stroke	Bilateral ICVs, VOG, STS later SSS and right SS	Bilateral basal ganglia and thalami edema later developed multifocal infarcts	**2.02**	3.52	LMWH	4
10	44/F	FND, AMS	> 14 d§ Severe	None	Left ICV, VOG, STS, torcula	NA	**5.98**	NA	LMWH	NA
11	65/ M	AMS, seizure	0 d Severe	None	Right TS, SS	Right temporal hemorrhagic infarct	NA	NA	Anticoagulant (NS)	0
12	54/ M	AMS,	15 d Severe	HTN	Bilateral ICVs, VOG, right BVR	Bilateral basal ganglia and thalami edema, transependymal flow, obstructive hydrocephalus, later had more hydrocephalus and progressive deep cerebral edema	**3.15**	4.29	UFH EVD	6
13	59/ M	Headache, FND	0 d Mild	DM, HTN	SSS, torcula, right TS, SS, IJV	No parenchymal involvement	NA	**4.9**	LMWH	≤ 2
14	30/ M	Seizure	0 d Mild	None	Right SPS, torcula, left TS, SS, proximal IJV	Small right temporal lobe hematoma, subarachnoid hemorrhage	**0.75**	NA	LMWH	0
15	51/ M	AMS, FND	18 d Critical	Immobilization in ICU	SSS, torcula	Right frontal and parietal hemorrhagic venous infarction with midline shift, cerebellar tonsillar herniation	NA	NA	NA	6
15	72/F	AMS, FND	30 d Critical	DM, HTN, asthma, Immobilization in ICU	SSS	Hemorrhagic infarct in right ACA, MCA, PCOM territories with significant cerebral edema and subfalcine, subtentorial and cerebellar tonsillar herniation	NA	NA	None, Supportive care	6‖
16	29/F	FND, seizure	7 d Severe	Severe iron deficiency anemia	Left TS, SS, IJV	Left temporoparietal hemorrhagic infarct, with mass effect	**2.88**	NA	LMWH	**2**
17	81/ M	AMS	A few days Critical	Prostate cancer, ocular MG B-CLL (in remission) Hemolytic anemia Immobilization in ICU	R SS	Bilateral subacute MCA infarctions, left M1 occlusion, right M2 occlusion	**2.02**	**5.39**	Anticoagulant (NS)	6‖

TABLE 2. (*continued*)

References	Age/ Sex	Presentation	Onset */COVID-19 status†	Thrombotic Risk Factors/ Medical Problems	Sinus/Vein Involvement	Brain Lesions	D-Dimer (mg/L)	Fibrinogen (g/L)	Initial Treatment	mRS at d/c
18	62/F	Headache, FND, AMS	15 d Severe	Morbid obesity	Bilateral ICVs, VOG, STS, left TS	Left frontotemporal ICH	**14.2**	NA	NA	NA
18	54/F	Headache	14 d Mild	Breast cancer on hormone replacement therapy	Left TS	Left temporal hemorrhagic infarction	**2.36**	NA	NA	NA
19	54/ M	FND then AMS	14 d Severe	None	Deep veins of the left hemisphere	Left basal ganglia, thalamo-capsular infarction with a small ICH at caudate nucleus with mass effect and midline shift later developed more cerebral edema and midline shift	**3**	**9.36**	LMWH Decompressive Surgery	6
20	63/F	FND, status epilepticus	12 d Severe	NA	STS, left TS, SS, IJV	Large left temporal ICH	NA	**7.2**	UFH, ICH evacuation, decompressive surgery	6
21	56/ M	Headache	12 d Severe	NA	Torcula, left TS	No parenchymal involvement	**10.3**	NA	UFH	0
22	17/ M	Headache, blurred vision	0 d Mild	Obesity	SSS, bilateral TS, STS, SS, IJV, left vein of Labbe	No parenchymal involvement	**1.13**	3.55	LMWH	0
22	72/F	FND	7 d Critical	Breast cancer in remission	Right TS, IJV	NA	NA	**5.09**	None	6‡
22	26/ M	Headache, FND	A few weeks/Mild	None	Right junction of Trolard vein with SSS	Right parasagittal ICH	NA	3.12	None	2
23	30/ M	Headache, FND	3 d Mild	NA	SSS, right TS	Right frontal hemorrhagic infarcts	**1.02**	NA	LMWH	≤2
24	18/ M	Headache	30 d§ Mild	None	STS, SSS	No parenchymal involvement	NA	Normal	LMWH	0
25	22/ M	AMS, seizure	NA Critical	None	SSS, left TS, STS, SS	Left hemispheric ischemic change with hemorrhagic infarct and cerebral edema with midline shift	NA	NA	LMWH, decompressive surgery	6
25	28/ M	Headache, AMS	3 d NA	None	Right TS, SSS	NA	NA	NA	LMWH	6
26	64/ M	Seizure	NA Critical	NA	Right TS, SS	Right parietal ICH	NA	NA	LMWH	NA
26	75/F	Headache, FND	NA NA	NA	NA	Left parietal ICH	NA	NA	LMWH	NA
26	52/ M	Headache, FND	NA NA	NA	NA	Right parietal ICH	NA	NA	LMWH	NA
26	65/ M	AMS	NA Critical	NA	NA	Right parieto-occipital and temporal ICH	NA	NA	LMWH	NA
26	61/F	AMS	NA Critical	NA	NA	Left parietal ICH	NA	NA	LMWH	NA
26	75/F	NA	NA Critical	NA	NA	Right temporal ICH	NA	NA	LMWH	NA
27	48/ M	Headache, FND, AMS	36 d Mild	None	Right parietal cortical vein, SSS	Right parietal ICH with vasogenic edema	**0.77**	2.89	LMWH	1

28	44/F	Headache, AMS	NA Mild	Migraine Familial hemochromatosis IBD	Bilateral ICVs, STS, BVR	Bilateral basal ganglia edema, acute left basal ganglia and right thalamus hemorrhagic infarcts and ICH	**1.9**	NA	LMWH	4
29	68/F	Headache, AMS	18 d§ Mild	None	Cortical veins, SSS, torcula, STS, VOG, Inferior sagittal sinus, ICVs, bilateral TS and SS, left IJV	Venous congestion	**6.71**	**5.07**	LMWH	0
29	79/F	Headache, AMS	3 d Mild	HTN	Right TS	No parenchymal involvement	**8.46**	3.93	LMWH	0
29	25/F	Headache, FND,	120 d§ Mild	Evan's syndrome ITP VWD Multiple ICH	SSS, bilateral TS	No parenchymal involvement	0.24	2.89	UFH	0
30	50/ M	AMS	NA NA	NA	Cortical vein, SSS, left TS, left SS, and left IJV	Left temporal ICH	NA	3.8	LMWH	0
31	30s/ M	Headache	1 d Mild	None	Left TS, left SS	No parenchymal involvement	NA	NA	Dabigatran	0
31	30s/ M	Seizure	1 d Mild	None	Left TS, left SS, left IJV	Left temporal ICH, edema and midline shift	**4.6**	NA	UFH, decompressive surgery	6
32	72/F	NA	NA NA	NA	Right TS, right jugular bulb	NA	**> 35**	**8.56**	NA	NA
Present case	38/F	Headache, AMS	7 d Mild	Migraine Vitamin B12 and D deficiency IBD Hx of DVT/PE	Bilateral ICVs, right BVR, VOG, STS, torcula, right TS, SS, IJV	Bilateral basal ganglia, thalami and hippocampal edema, venous infarcts, mild hydrocephalus	2.27	4.82	LMWH EVD	1

Bold values indicate higher than normal range.
*Onset of COVID-19 symptoms to CVST symptoms.
†Wu and McGoogan.[33]
‡Died from respiratory failure secondary to critical COVID-19 infection.
§Negative COVID-19 status at CVST presentation.
||Probably died from combination with massive ischemic strokes.

ACA indicates anterior cerebral artery; AMS, altered mental status; BVR, Basal vein of Rosenthal; d/c, discharge; CVST, cerebral venous sinus thrombosis; d, day; DM, diabetes mellitus; DVT, deep vein thrombosis; EVD, external ventricular drainage; F, female; FND, focal neurological deficit; HTN, hypertension; IBD, Inflammatory Bowel Disease; ICH, intracerebral hemorrhage; ICV, internal cerebral vein; IJV, internal jugular vein; IVH, intraventricular hemorrhage; LMWH, low molecular weighted heparin; M, male; MCA, middle cerebral artery; mRS, modified-Rankin Scale; NA, not available; NS, not specified; OCP, oral contraceptive pill; PCOM, posterior communicating artery; PE, pulmonary embolism; SS, sigmoid sinus; SSS, superior sagittal sinus; STS, straight sinus; TS, transverse sinus; UFH, unfractionated heparin; VOG, vein of Galen; VWD, Von Willebrand disease.

TABLE 3. Summary of Clinical Presentations, COVID-19 Severity, Thrombotic Risk Factors and Imaging Findings of CVST Associated With COVID-19 Patients

Presenting symptoms (N = 41), n (%)	
Altered mental status	23 (56)
Headache	20 (49)
Focal neurological deficit	17 (41)
Seizure	10 (24)
COVID-19 severity[33] (N = 38), n (%)	
Mild	19 (50)
Severe	8 (31)
Critical	11 (29)
Thrombotic risk factors (N = 32), n (%)	14 (44)
Obesity	4 (13)
Hematological disease	4 (13)
OCP	3 (9)
Immobilization	3 (9)
Inflammatory bowel disease	2 (6)
Dehydration	1 (3)
Hormone replacement therapy	1 (3)
Radiologic findings (N = 38), n (%)	
Sinus/vein involvement	
Multiple	33 (87)
Superficial venous system	23 (61)
Deep venous system	5 (13)
Both superficial and deep venous systems	10 (26)
Transverse sinus	24 (63)
Sigmoid sinus	16 (42)
Superior sagittal sinus	14 (37)
Straight sinus	12 (32)
ICV/BVR/VOG	11 (29)
Internal jugular vein	11 (29)
Torcular	8 (21)
Cortical veins	7 (18)
Sphenoparietal sinus	1 (3)
Inferior sagittal sinus	1 (3)
Brain lesions (N = 39), n (%)	
Parenchymal involvement	31 (79)
Hemorrhagic conversion/intracerebral hemorrhage	24 (62)
Vasogenic edema	15 (38)
Venous infarct	13 (33)
Arterial ischemic stroke	2 (5)
No parenchymal involvement	7 (18)
Hydrocephalus	3 (8)
Subarachnoid/intraventricular hemorrhage	3 (8)

BVR indicates Basal vein of Rosenthal; CVST, cerebral venous sinus thrombosis; ICV, internal cerebral vein; VOG, vein of Galen.

possible etiologies.[27,31] In addition, relatively low numbers or patients and incomplete data available in the literature limit the scope of assessing the true impact on mortality from COVID-19 CVST.

Patients with CVST and COVID-19 more frequently present with altered mental status, in comparison to headache being the most common presentation for isolated CVST.[34,35] Radiographically, involvement of the deep cerebral venous system was more common (39% vs. 10.9%), parenchymal changes were more frequent (79% vs. 40.1% to 62.9%) and hemorrhagic transformation or hemorrhagic stroke was more common (63% vs. 21.1%) in patients with COVID-19 infection and CVST. Fewer patients had identified thrombotic risk factor (44% vs. 85%), suggesting that COVID-19 itself might be a risk factor.[35,37,38] COVID-19 infection is a possibly provoking factor for CVST in patients with thrombotic risk factors, though the exact mechanism is not clear.[29]

Like our findings, a multinational case series of 13 CVST associated with COVID-19 showed that these patients were older (mean age 50.9 y) and had higher mortality (23.1% vs. 5.3%). This study also showed that CVST diagnosis was not associated with severity of other COVID-19 systemic symptoms (23.1% vs. 5.3%). However, most patients in this series were female (61.5%), headache was the most frequent presentation (83.3%) and < 25% of patients had identified thrombotic risk factors.[39] Before the pandemic, active or recent infection accounted for ~ 10% of adult cases with CVST especially in developing countries.[34] However, viral infections associated with CVST remain rare, with the most commonly reported being herpes virus and human immunodeficiency virus.[7]

Though the prothrombotic mechanisms of COVID-19 are not fully understood, prior studies have postulated mechanisms including endothelial damage by the virus itself or the cytokine storm produced by the hyperinflammatory state.[2,40] In addition, the angiotensin-converting enzyme receptor 2 receptor, also a functional receptor for COVID-19, is found in endothelial cells, glial cells and neurons in the CNS. The angiotensin-converting enzyme receptor 2 has been detected in CSF by rt-PCR and in the neurons and brain endothelial cells in the brain tissue on autopsy in prior case reports.[3] Antiphospholipid antibodies have been reported in COVID-19 patients with stroke, however, the significance of antiphospholipid in hypercoagulable tendency of COVID-19 patients is uncertain and requires further studies.[36] They can be transient or persistent elevation after the viral infections, which was also noted in this series of CVST patients.[28]

Like other patients in the literature, our present case showed elevation in acute phase reactants (d-dimer and FVIII activity) at presentation, but she had thrombocytosis and normal coagulation studies. Prior studies in the literature have shown that the most typical laboratory abnormalities in patients with COVID-19 associated coagulopathy are an increased D-dimer concentration, mild thrombocytopenia, and a slight prolongation of the prothrombin time.[40] An increased D-dimer was found to be correlated with severity of the disease and mortality.[40] Other coagulopathy findings in the reported literature include increases in fibrinogen, fibrin degradation products and factor VIII levels and reduction in antithrombin III (AT III) level.[40]

Early initiation of AC is the key treatment for CVST. Current evidence suggests LMWH may be more favorable than UFH in several regards, because of predictable pharmacokinetic profile, better safety (reduced rate of new associated hemorrhage and thrombotic complications), and better efficacy (reduced mortality and better functional outcome). An additional advantage during the pandemic, LMWH allows reduced staff exposure to COVID-19 as UFH requires frequent blood draws to monitor PTT.[41] The 2017 European Stroke Organization guideline for the diagnosis and treatment of CVST, endorsed by the European Academy of neurology, recommended "LMWH over UFH except in patients who are allergic to LMWH, or if fast anticoagulant effect reversal is required."[42] Similar to our patient, White and colleagues found heparin resistance with UFH (> 35,000 units/day) and suboptimal anti-Xa peak with LMWH in 80% and 100% of COVID-19 intensive care unit patients, respectively. The effects of increased fibrinogen and factor VIII with low AT could contribute to heparin resistance.[43] Careful monitoring of PTT or anti-Xa levels to ensure adequate dosing are recommended.

The most common cause of death in CVST patient is transtentorial herniation, though it is not entirely clear from the current series if this was underlying the higher mortality seen with COVID-19 CVST. Close monitoring of clinical and hemostatic markers (the platelet counts, PT, D-dimer, and

TABLE 4. Comparison of CVST Associated With COVID-19: Patients With Good Versus Poor Outcomes and Alive Versus Death Outcomes

Variable	Good Outcome mRS ≤ 2 (N = 17), n (%)	Poor Outcome mRS > 2 (N = 16), n (%)	*P*	Alive (N = 20)	Death (N = 13)	*P*
Demographic						
Age (mean ± SD)	41.94 ± 19.08	55.13 ± 17.73	0.0560	44.7 ± 19.2	54 ± 18.9	0.1987
Male	11 (52.4)	10 (47.6)	0.8953	12 (57.1)	9 (42.9)	0.5902
Clinical						
FND	6 (40)	9 (60)	0.2269	8 (53.3)	10 (46.7)	0.4351
AMS	6 (33.3)	12 (66.7)	**0.0221**	8 (44.4)	10 (55.6)	**0.0374**
Headache	13 (81.2)	3 (18.8)	**0.0009**	14 (87.5)	2 (12.5)	**0.0022**
Seizure	4 (44.4)	5 (55.6)	0.6187	5 (55.6)	4 (44.4)	> 0.999*
COVID-19 severity						
Severe/critical	3 (23.1)	10 (76.9)	**0.0069**	3 (23.1)	10 (76.9)	**0.0002**
Thrombotic risk factors						
Identified	5 (41.7)	7 (58.3)	0.4561	7 (58.3)	5 (41.7)	> 0.999*
Radiological findings						
Superficial venous thrombosis	15 (65.2)	8 (34.8)	**0.0169**	16 (69.6)	7 (30.4)	0.1393*
Deep venous thrombosis ± superficial venous thrombosis	2 (20)	8 (80)	**0.0169**	4 (40)	6 (60)	0.1393*
Venous infarct	4 (33.3)	8 (66.7)	0.0559	7 (58.3)	5 (41.7)	0.7054*
Vasogenic edema	5 (33.3)	10 (66.7)	**0.0198**	7 (46.7)	8 (53.3)	**0.0443**
ICH	7 (43.8)	9 (56.3)	0.2001	9 (56.3)	4 (43.8)	0.3205
Laboratory findings						
D-dimer level (mg/L) (mean ± SD)	1.75 ± 2.99	8 ± 17.69	0.3241	1.86 ± 2.79	10.87 ± 21.65	0.3559
Fibrinogen level (g/L) (mean ± SD)	3.91 ± 0.82	5.22 ± 2.42	0.1833	4.03 ± 0.91	5.42 ± 2.75	0.2761

Bold values are the levels of significance for the respective analysis.

*Fisher test.

AMS indicates altered mental status; COVID-19, coronavirus disease 2019; CVST, cerebral venous sinus thrombosis; FND, focal neurological deficit; ICH, intracerebral hemorrhage; mRS, modified-Rankin scale.

fibrinogen) is strongly recommended to identify worsening intracranial hypertension and coagulopathy.[38,44] Since poor outcomes are associated with older age, severe COVID-19 infection, and presentation with altered mental status, we recommend paying special attention in these group of patients and consider screening for CVST if other etiologies for encephalopathy have been excluded.

Patients with severe CVST associated malignant cerebral edema may benefit from lifesaving decompressive surgery, and it can offer favorable outcomes.[45] The evidence for endovascular treatment in CVST is limited. The Society of Neurointerventional Surgery recommended that endovascular therapy may be considered in patients with clinical deterioration despite AC, or with severe neurological deficits or coma (class IIb; level of evidence C).[45] It is unclear from this series if these approaches to management (decompression, endovascular) should be used for COVID-19 CVST, considering all of the patients who underwent these treatments did not survive. However, such a conclusion to defer consideration of these treatments cannot necessarily be drawn from this series, because of the lack of power from low patient numbers, and a lack of systematized treatment paradigm. Traditionally, both decompressive surgery and endovascular treatments are offered for CVST patients failing AC treatment. To measure the extent of impact they may impact on survival and outcome in CVST, whether COVID-19 related or not, would likely require earlier employment, rather than as a final treatment option when other approaches have failed.

In summary, during this pandemic, patients who presents with unusual headache, altered mental status, focal neurological deficit, or new onset seizure, unusual parenchymal hemorrhage or infarction, regardless of age, sex or prothrombotic risk factors, should be tested for COVID-19 and CVST. CVST may be underdiagnosed in the ICU setting given prolonged mechanical ventilator and sedation limiting access to imaging and frequency of neurological assessment. COVID-19 patients with encephalopathy without hypoxia or those who have a hard time weaning off the ventilator, and high D-dimer levels should have early neurological evaluation.[3] The mortality from COVID-19 associated CVST is very high in this series, early diagnosis and prompt treatment will likely affect the outcome of these patients.

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