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CEREBRAL VENOUS SINUS THROMBOSIS ASSOCIATED WITH CORONAVIRUS INFECTION (COVID-19)

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ABSTRACT:

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome (SARS) caused by the SARS-CoV-2 coronavirus. Despite its primarily respiratory involvement, an increased propensity for systemic inflammation, neuroinvasion, and thromboembolic events has been reported. This systemic prothrombotic state may predispose to cerebral venous sinus thrombosis (CVST), which is an uncommon cerebrovascular disease with hypercoagulability as one of its important risk factors. We conducted a literature search using the PubMed electronic database and reviewed the published literature for a possible association of CVST with the COVID-19 disease.

Keywords: Cerebral venous thrombosis; CVST; COVID–19; Coronavirus; SARS-CoV-2

Introduction

The first case of coronavirus disease 2019 (COVID-19) was diagnosed on December 8, 2019, in Wuhan city of central China.[1] It is a severe acute respiratory syndrome (SARS) caused by the SARS-CoV-2 coronavirus. The World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic on March 11, 2020. More than 12.5 million confirmed cases and over 550,000 deaths have been reported worldwide, as of July 12, 2020.[2]. Neurological manifestations in COVID-19 have been reported from early features of anosmia and dysgeusia to widespread involvement of the central nervous system (CNS), peripheral nervous system (PNS), and the muscle.[3] Multiple studies have suggested an increased propensity among COVID-19 patients to systemic thromboembolism.[4-6] An increase in cerebrovascular diseases (1-6%) has also been reported among COVID-19 patients.[7] However, the available data regarding the cerebral venous sinus thrombosis (CVST) in COVID-19 patients is generally limited. The purpose of this article is to review the available literature regarding the CVST cases in COVID-19 patients and look for a possible correlation.

MATERIALS AND METHODS:

An online literature search was conducted through the Medline (PubMed) database. We used the following search keywords terms: “CVST” or “CVT” or “cerebral venous thrombosis” or “cerebral venous sinus thrombosis” and “COVID-19” or “coronavirus”. We included the articles that were published in English and published from 1st January 2020 to 30th June 2020. Our search retrieved a total of 20 results. 7 results out of 20 were excluded due to unrelated title and abstract, short commentaries, and duplicate results. Finally, 13 full-text articles were included in this review.

RESULTS

A total of seven case reports and two case series were included in this review. Both case series consisted of a total of five cases, making the total subject count to 12. All cases tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT PCR) assay of a nasopharyngeal swab. Out of 12 subjects, 7 were male (58%) and 5 were female (42%). The average age was 52.2 years with a range of 23-81 years. In 9 out of 12 cases, the diagnosis of CVST was confirmed by a venogram, while in the remaining 3

patients the diagnosis of CVST was suspected based on the characteristic CT and/or MRI findings.[8-10] One case had concomitant arterial and venous thrombosis.[9] Two female cases were on oral contraceptives,[8,10] one female was on hormonal therapy for breast cancer,[11] and one male case had a history of ocular myasthenia, prostate adenocarcinoma, and B-cell chronic lymphocytic leukemia.[9] Headache and altered mentation (67%) were the most common neurological features among these patients, followed by hemiparesis (33%), aphasia (25%), and seizures (17%) with one case having status epilepticus (8%). Five cases (42%) presented with either headache or altered mentation or both.[8,9,11,13] Four patients (33%) did not have respiratory symptoms at the time of diagnosis of CVST.[8,10,12,13] A clinical outcome of 8 cases has been mentioned. Five out of eight cases (62%) died while three cases (38%) were discharged home with improving conditions (Table 1).

DISCUSSION

COVID-19 is a novel infection that primarily affects the respiratory system but it is known to affect almost all the systems of our body, including the nervous system. The most common reported neurological manifestations of COVID-19 patients are anosmia (5.1 % – 85.6%) and dysgeusia (5.6% - 88%) followed by headache (8%) and dizziness (7-9%).[3] Cerebrovascular diseases (1% - 6%) are also reported in COVID-19 patients especially with the severe COVID-19 disease (2.5-fold increase in odds).[7] Ischemic stroke mainly from large-vessel occlusion is the most commonly reported type of cerebrovascular disease.[7] A similar pooled data regarding the CVST is presently lacking. Hypercoagulable state is one of the important risk factors for CVST.[17] COVID-19 may also predispose the patients to a systemic hypercoagulable state. In a retrospective study, a 31% incidence of thrombotic complications is reported in Dutch patients (n=184) with severe COVID-19 admitted in the intensive care unit (ICU) including 3 patients with stroke, with pulmonary embolism being the most common thrombotic complication among them (n=25, 81%). The independent predictors of thrombotic complications in these patients were advanced age and coagulopathy, which is defined as spontaneous prolongation of PT/APTT (prothrombin time > 3 s or activated partial thromboplastin time > 5 s).[4] Another retrospective study from Italy (n=388) reported a high incidence of venous thromboembolism (21%) in COVID-19 patients.[5] In France, a retrospective study revealed a higher incidence (11.7%) of thrombotic complications in COVID-19 patients with acute respiratory distress syndrome (ARDS) (n=150) as compared to the control group of non-COVID-19 ARDS patients (2.1%).[6] Almost all the patients were receiving standard thromboprophylaxis in these studies. It is surprising that despite an increased incidence of systemic thrombotic complications, no cases of CVST were reported in these studies. However, an underestimation cannot be excluded. In our review, 4 out of 12 patients (33%) already had the risk factors for CVST. A thrombophilia workup was only performed for 4 patients (33%), which was negative.[10,13-15] Due to the lack of available data at present, a causal relationship between the COVID-19 and CVST cannot be definitely made. Five cases (42%) presented with either headache or altered mentation or both.[8,9,11,13] Therefore, we suggest that there should be a low threshold for ordering venogram to exclude CVST in COVID-19 patients presenting with headache and/or altered mentation. Interestingly, four patients (33%) did not have respiratory symptoms at the time of diagnosis of CVST.[8,10,12,13] Presuming many patients with COVID-19 are asymptomatic, all patients with newly diagnosed CVST should undergo a nasopharyngeal swab testing for SARS-CoV-2 RT-PCR or a CT scan of the chest scan to look for COVID-19 infection in the current pandemic situation.

PATHOPHYSIOLOGY

Multiple pathophysiological mechanisms for SARS-CoV-2 infectivity have been proposed. The interaction between the SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors has been proposed as one of the important potential factors in its infectivity. SARS-CoV-2 gains entry into our body through ACE2 receptors and later also down-regulates ACE2 expression. ACE2 receptors are present in the respiratory tract as well as in the endothelial lining of the heart, intestines, kidney, and brain.[1,3,18] A direct neuroinvasion through the nasal epithelium and olfactory bulb with subsequent retrograde spread has been proposed. Netland et al. [19] conducted an experiment on transgenic mice expressing the human ACE2 receptors and infecting them with SARS-CoV. The authors reported viral entry into the brain primarily via the olfactory bulb with further spread within the CNS. They also reported significant neuronal injury with relatively limited inflammation suggesting a possibility that inflammatory signs may be minimal or even absent in these patients. The detection of cerebrospinal fluid RT-PCR for SARS-CoV-2 in a few cases [20-21] also hints to the direct neuroinvasion of SARS-CoV-2. Another proposed theory is based on the findings of viral endotheliitis in the postmortem

examinations of COVID-19 patients.[22] The direct viral invasion of endothelial cells may cause widespread endothelial dysfunction resulting in procoagulant state and multiorgan vascular involvement as seen in severe COVID-19 infections.[1] Further, severe COVID-19 infections may also increase the risk for thromboembolic disease due to excessive systemic inflammation, hypoxia, hypotension and inadequate cerebral perfusion, immobilization, and diffuse intravascular coagulation, with very high serum levels of C reactive protein, D-dimer, ferritin, fibrinogen, and fibrinogen degradation product.[1,3] Antiphospholipid antibodies (anticardiolipin IgA and antibodies directed against β2-glycoprotein-1) have also been found in patients with COVID-associated large vessel ischemic strokes, which may further increase the risk of thrombotic disease.[23]

LIMITATIONS

The main limitation is the small number of available cases. We believe that the number of CVST cases are an underestimation. Many CVST cases may present with nonspecific symptoms such as headache and altered mentation, which need to be evaluated in these patients. The systemic thrombophilia workup was also absent in the majority of the cases. The severe COVID-19 patients are also administered multiple drugs. The effects of these drugs on coagulation need evaluation. Further, the confounders such as dehydration and anemia, are not adjusted. They independently increase the risk of CVST and are commonly present in severely ill patients.

FUTURE DIRECTIONS

We are still learning about the neurology of COVID-19. Epidemiological studies are required to provide an estimation of the total numbers of CVST cases, including the mild ones. The risk factors, drug effects, behaviors, and outcomes need to be evaluated. The neurotropic potential of SARS-CoV-2 has to be understood and the frequency of its complications, including but not limiting to the cerebrovascular diseases, has to be reported for early diagnosis and management.

CONCLUSIONS

The limited data suggest that the COVID-19 may predispose patients to CVST secondary to the high incidence of systemic thromboembolism. However, large studies are needed to confirm a possible causal relationship between CVST and COVID-19 infection. We suggest a venogram should be performed in COVID-19 patients presenting with altered mentation and/or headache, with or without focal neurological deficits, to exclude CVST. Similarly, patients presenting with acute CVST in the current pandemic should be evaluated for COVID-19.

Table 1: CVST Cases

S.No	Author/Month	Age/Gender	PMH	Neurological features	Time from respiratory symptoms	Vessels involved	Thrombophilia Testing	Other CVST Risk Factors	CVST Treatment	Outcome
1	Hughes et al., April 2020 [12]	59 M	DM, HTN	HA, dysarthria and dysphasia	Absent	Rt. TS and Rt. SS	N/A	Increased BMI	LMWH followed by apixaban 10 mg BID	Survived. Discharged home.
2	Malentacchi et al., May 2020 [9]	81 M	Ocular MG, TURP for adenocarcinoma, B-CLL, and recently treated hemolytic anemia	AM	Few days	Bil. MCAs & Rt. SS	N/A	None	Anticoagulation	Death
3	Poillon et al., May 2020 (n=2) [11]	62 F	None	HA, Rt. HP, AM, and altered vision	2 weeks	Lt. TS, straight vein, vein of Galen and DCVs	N/A	Increased BMI	N/A	N/A
4		55 F	Breast cancer in remission, on hormone therapy	HA	2 weeks	Lt. TS	N/A	None		N/A
5	Hemasian et al., May 2020 [13]	65 M	None	AM	Absent	Rt. SS and Rt. TS,	Negative	None	Anticoagulation	Survived. Discharged home
6	Garaci et al., May 2020 [14]	44 F	None	HA, AM, aphasia and Rt. HP	2 weeks	vein of Galen and straight sinus	Negative	None	N/A	N/A
7	Coline et al., June 2020 [10]	33 F	None	HA, anosmia, dysgueusia and seizure	Absent at the time of headache	Lt. parietal cortical CVST Venogram N/A	Negative	combined estrogen-progestin OC Increased BMI	dabigatran 150mg BID	Survived. Discharged home
8	Chougharet al., June 2020 [15]	72 M	None	Lt. HP, AM, and refractory status epilepticus	Few days	DCV	Negative	None	Anticoagulation	Death
9	Rigamonti et al., June 2020 [16]	54 M	None	HA, aphasia, Rt. hemianopsia, and Rt. HP	2 weeks	DCV	N/A	None	LMWH	Death
10	Cavalcanti et al., June 2020 [8] (n=3)	38 M	ASD	HA and AM	Absent	Rt. ICV	N/A	Dehydration	LMWH + Thrombectomy	Death
11		41 F	None	Confusion and aphasia	N/A	ICV, vein of Galen and distal straight sinus	N/A	Estrogen-containing OC	Heparin Infusion	Death
12		23 M	New-onset DM with DKA	HA and AM	Present but time out specified	Venogram not done. CT Head, CTA and MRI Brain are suggestive of CVST	N/A	Dehydration	N/A	Death

Abbreviations:

AM = Altered mentation; ASD = Autism spectrum disorder; B-CLL = B-cell chronic lymphocytic leukemia; Bil. = Bilateral; BMI = Body mass index; CVST = Cerebral venous sinus thrombosis; DCV = Deep cerebral veins; DM = Diabetes mellitus; F = female; HA = Headache; HP = Hemiparesis; HTN = Hypertension; ICV = Internal cerebral veins; LMWH = Low molecular weight heparin; Lt. = Left; M = male; MCA = Middle cerebral artery; MG = Myasthenia gravis; N/A = not available; PMH = Past medical history; Rt. = Right; TS = Transverse sinus; SS = sigmoid sinus; TURP = Transurethral resection of the prostate

References:

1. Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. Ann Neurol. 2020 Jun 7;10.1002/ana.25807

2. Johns Hopkins University Coronavirus Resource Center. [Online]. Available from: https://coronavirus.jhu.edu/ [Accessed 12 July 2020].

3. Román GC, Spencer PS, Reis J, Buguet A, et al. The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. J Neurol Sci. 2020 Jul 15;414:116884. 10.1016/j.jns.2020.116884

4. Klok FA, Kruip MJ, Van der Meer NJ, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020 Jul;191:145-147. 10.1016/j.thromres.2020.04.013

5. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020 Jul;191:9-14. 10.1016/j.thromres.2020.04.024

6. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098. 10.1007/s00134-020-06062-x

7. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. Int J Stroke. 2020 Jun;15(4):385-389. 10.1177/1747493020921664

8. Cavalcanti DD, Raz E, Shapiro M, et al. Cerebral Venous Thrombosis Associated with COVID-19. AJNR Am J Neuroradiol. 2020 Jun 18. 10.3174/ajnr.A6644

9. Malentacchi M, Gned D, Angelino V, et al. Concomitant brain arterial and venous thrombosis in a COVID-19 patient. Eur J Neurol. 2020 Jun 5;10.1111/ene.14380. 10.1111/ene.14380

10. Coline B, Thierry D, Amandine K, Nathalie M, Pierre RM. COVID-19 as triggering co-factor for cortical cerebral venous thrombosis? J Neuroradiol. 2020 Jun 27;S0150-9861(20)30205-4. 10.1016/j.neurad.2020.06.008

11. Poillon G, Obadia M, Perrin M, Savatovsky J, Lecler A. Cerebral Venous Thrombosis associated with COVID-19 infection: causality or coincidence? J Neuroradiol. 2020 May 11;S0150-9861(20)30167-X. 10.1016/j.neurad.2020.05.003

12. Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral Venous Sinus Thrombosis as a Presentation of COVID-19. Eur J Case Rep Intern Med. 2020 Apr 29;7(5):001691. 10.12890/2020_001691

13. Hemasian H, Ansari B. First case of Covid-19 presented with cerebral venous thrombosis: A rare and dreaded case. Rev Neurol (Paris). 2020 Jun;176(6):521-523. 10.1016/j.neurol.2020.04.013

14. Garaci F, Giuliano FD, Picchi E, Ros VD, Floris R. Venous cerebral thrombosis in COVID-19 patient. J Neurol Sci. 2020 Jul 15; 414:116871. 10.1016/j.jns.2020.116871

15. Chougar L, Mathon B, Weiss N, Degos V, Shor N. Atypical Deep Cerebral Vein Thrombosis with Hemorrhagic Venous Infarction in a Patient Positive for COVID-19. AJNR Am J Neuroradiol. 2020 Jun 18. 10.3174/ajnr.A6642

16. Rigamonti A, Mantero V, Piamarta F, Spena G, Salmaggi A. Cerebral venous thrombosis associated with coronavirus infection: an underestimated entity? Neurol Sci. 2020 Jun 29;1-2. 10.1007/s10072-020-04539-7

17. Wasay M, Kaul S, Menon B, et al. Asian Study of Cerebral Venous Thrombosis. J Stroke Cerebrovasc Dis. 2019 Oct;28(10):104247. 10.1016/j.jstrokecerebrovasdis.2019.06.005.

18. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020 Apr 23;382(17):1653-1659. 10.1056/NEJMsr2005760

19. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human

ACE2. J Virol. 2008 Aug;82(15):7264-75. 10.1128/JVI.00737-08

20. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55–58.

21. Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun 2020. 10.1016/j.bbi.2020.05.012

22. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020 May 2;395(10234):1417-1418. 10.1016/S0140-6736(20)30937-5

23. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020 Apr 23;382(17):e38. 10.1056/NEJMc200757

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