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Characteristic Cerebral Venous Thrombosis (CVT) in COVID-19: A Systematic Review

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Abstract

Cerebral venous thrombosis (CVT) is one of the diagnoses reported in coronavirus disease 2019 (COVID-19 patients). Meanwhile, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has the potential to cause endothelial dysfunction, increase thrombin generation and inhibit fibrinolysis. This causes hyper coagulopathy, with the potential to become CVT. Therefore, this study aims to determine the characteristics of CVT cases in COVID-19 patients. This systematic review refers to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines. The articles were obtained systematically from online databases, Pubmed, Science Direct, as well as Google Scholar, using the search keywords ("COVID 19" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019-nCoV infection" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019- nCoV disease "OR" COVID-19 virus infection") AND" cerebral venous thrombosis " as well as " cerebral venous thrombosis ".

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After deduplication, eligibility criteria selection and critical assessment on journals, the study reviewed eight patients from four case reports and two case series. According to the characterization, CVT patients with COVID-19 had a mean age of 42.4 years, were mostly male, tended to be cryptogenic, as well as varied neurological symptoms, and increased D-Dimer in most cases. All patients showed CVT features on imaging and were treated using mostly anticoagulants. Five out of the eight patients (50%) died.

Keywords: *Cerebral Venous Thrombosis, characteristic, and COVID-19*

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused the coronavirus disease 2019 (COVID-19) pandemic, which started in Wuhan, China in December 2019. The common presenting symptoms and signs include fever, cough and shortness of breath. Furthermore, some typical pulmonary findings have been observed on chest CT and chest radiographs (Goldberg *et al.*, 2020).

The neurologic manifestations extend from mild to severe, including impaired consciousness, acute cerebrovascular disease, and seizures. A recent study reported a presumptive case of COVID-19–associated acute necrotizing haemorrhagic encephalopathy, while an increased associated risk of cerebrovascular complications was most common. Moreover, literature reports showed an extensive deep cerebral vein thrombosis with haemorrhagic venous infarction in a patient having positive diagnostics for SARS-CoV-2, with no known thrombosis risk factor (Chougar *et al*., 2020).

There has been an increase in attention towards the common complication of patients with COVID-19 infection, including the disseminated intravascular coagulation (DIC), observed in critically ill sufferers. Furthermore, recent DIC reports in a patient affected by 2019-nCoV showed severe complications as a poor prognosis, which is implicated in increased mortality (71.4% of patients who died of COVID-19) (Garaci *et al.*, 2020).

Recent studies have reported the potential development of a hypercoagulable state in COVID-19 patients. Moreover, viral infections are estimated to promote the dysfunction of endothelial cells, and instigate excess thrombin generation, alongside fibrinolysis inhibition. The incidence of hypoxemia is closely associated with an elevation in blood viscosity, and also the activation of hypoxia-related genes. This cascade of events mediate coagulation and fibrinolysis, to consequently favour thrombotic events. Particularly, cerebral venous thrombosis (CVT) presents with a broad variety of neurologic signs and symptoms (Cavalcanti *et al*, 2020).

Therefore, a systematic review is performed on these studies to understand the risk of hypercoagulopathy on the potential for CVT, and to also recognize clinical manifestations in CVT. Hence, this research is expected to help physicians with proper diagnosis and management.

2. Material and Methods

This systematic review was prepared by adjusting the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines. Furthermore, relevant articles were obtained from online databases: Pub med, Science Direct and Google Scholar, and the keywords used include

("COVID-19" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019-nCoV infection" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection") AND "cerebral venous thrombosis".

The synthesized articles were selected based on the following eligibility criteria: Those with a mention of CVT disease, suggesting links between CVT with COVID-19. In addition, other parameters include the absence of any age, gender, national or racial restrictions, and only empirical research (not review articles) items in English, and all quantitative research designs were used. The literature searches were not limited to a specific time, considering the incidence case was in 2019. Therefore, all documents reviewed are expected to have been written on topics within this time frame.

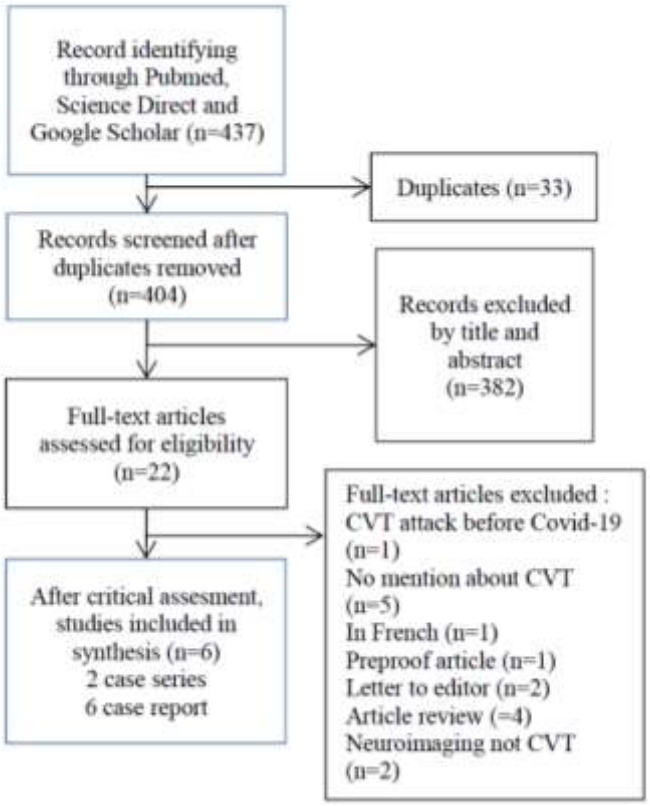

Figure 1: Prisma flow chart

A literature search through an online database on 6 August 2020 identified 437 journals. Therefore, a screening exercise was performed jointly by four researchers observing the duplication and relevance through titles and or abstracts. Subsequently, a total of 33 were excluded on the basis of being duplications, while 382 were removed for being irrelevant. Furthermore, a rescreening was conducted by reading each journal's index based on eligibility criteria, on a total of 22 journals. The discussion between four researchers further resolved the dissent in determining the articles' suitability, and those determined to be relevant were subjected to critical appraisal using an

instrument, following the study design. Consequently, sixteen more were excluded because CVT was mentioned before COVID-19 (1), CVT cases were not discussed (5), and also for being written in French-language journals (1), pre-proof articles (1), letters to the editor (2), review articles (4) and because CVT was not revealed during neuroimaging. Furthermore, 8 cases from 2 case series and 4 case reports were analyzed narratively.

3. Results

This study analysed the demographics of clinical, laboratory (D-dimer) manifestations, neuroimaging, therapy, and CVT case outcomes in COVID-19 patients. The results are shown in tables 1 and 2.

This study identified the mean age of CVT patients with COVID-19 at 42.37 years, with a range of 23 - 65 years. However, there were more male patients (5/8) than females (3/8). In addition, a total of three individuals experienced comorbidities, including hypertension, mild autism, and oral contraceptives, while the neurological symptoms varied from mild to severe.

Table 1: The results of demographic studies and clinical characteristics of CVT cases in COVID-19 patients

No.	Author	Demographic comorbid	Signs & Symptoms
1	Kananeh MF *et al*, 2020	54, male, hypertension	Coma, dyspnea, cough, hypoxia
2	Cavalcanti DD *et al*, 2020	38, male, mild autism	mental state disorder, gastroenteritis, vomit
3	Cavalcanti DD *et al*, 2020	41, female, no comorbid	confuse, global aphasia, left gaze preference, unconsciousness
4	Cavalcanti DD *et al*, 2020	23, male, no comorbid	headache, lethargie, myalgia, fever, dry cough
5	Sugiyama Y *et al*, 2020	56, male, no comorbid	headache, malaise, fever, vomit
6	Klein DE *et al*, 2020	29, female, no comorbid	Seizure, mildly agitated, neck pain, decreased of consciousness, aphasia, decreased blink reflex and facial palsy on the right side, paralysis in all four limbs with slightly less movement of the right upper extremity, bilateral 6th nerve palsies and bilateral papilledema, cough, fever, mild dyspnea and headache.
7	Baudar C *et al*, 2020	33, female, oral contraception	headache, myalgia, dysgeusia, anosmia, partial complex seizure, fever, dyspnea,
8	Hemasian *et al*, 2020	65, male, no comorbid	unconsciousness, upward gaze palsy, tongue biting

Table 2: Laboratory findings, neuroimaging, therapy and outcome of CVT cases in COVID-19 patients

No.	D-dimer	Imaging	Therapy	Outcome
1	7873	Brain MRI and CT Venogram (filling defect in the bilateral internal cerebral veins, Galen vein, straight sinus and right basal vein of Rosenthal)	External ventricular drain, Heparin drip	Death
2	No data	Brain CT Venogram (thrombosis in the superior sagittal, right transverse, and sigmoid sinuses).	Thromboectomy, a microcatheter was left in the superior sagittal sinus with an infusion rate of 2 mg/h of tPA.	Death
3	2032	Brain CT venogram (thrombosis in the Galen, internal cerebral and the inferior sagittal sinuses)	External ventricular drain, Heparin infusion	Death
4	> 11.000	T2 and T2 weighted images of brain MRI (the generalized low intensity of the white matter, and impaired outflow of the deep medullary venous)	Intubation	Death
5	10,3	T2 FLAIR-weighted Brain MRI (hyperintense area in left transverse sinus)	UFH i.v, Edoxaban 60 mg	Discharged and reported free of symptoms 14 days thereafter
6	2876	Brain MR venography (absence of flow in the left tranversus - sigmoid sinuses and sigmoid sinus and thrombosis in the left internal jugular vein)	Intravenous heparin. Enoxaparin 50 mg s.c/12 h Asetazolamid	No data
7	902	Cortical CVT is shown in FLAIR (hyposignal due to deoxyhemoglobin), in pre-contrast T1 weighted (hypersignal due to methemoglobin) and in post-contrast T1-weighted (hyposignal due to the signal intensity switch featuring the so-called "delta sign")	Dabigatran 150 mg twice/day.	Complete relief of headaches five days upon initiation of anticoagulation

8	No data	Brain CT - hemorrhagic infarct in right temporal lobe; MR venography - right sigmoid and transverse sinus thrombosis	Anticoagulant, Co-amoxiclav, Hydroxychloroquine, Levetiracetam	Discharged at day-10 in good health

4. Discussion

The previous study showed development of thromboembolic complications in 5-15% of patients with severe COVID-19 (Michael K *et al.*, 2018). Based on the 8 case reports, five patients were under 50 years, while 3 were above. In addition, the mean age of CVT patients with COVID-19 recorded was 42.4 years, within the range of 23 - 65 years. Previous studies have shown the occurrence of CVT at a young age, with an incidence of around 3-4 million young adults, and 7 million children (Michael *et al.*, 2018). Furthermore, the comparison ratio based on sex was 5: 3 for male to female, which is different from previous reports, where women with CVT were more at (3: 1). It is possibly influenced by hormonal factors (Hernando *et al.*, 2013). Based on the comorbidity aspects in COVID-19 patients, 3 cases were recognized, including hypertension, mild autism, and oral contraceptives, while five patients had none.

The neurological manifestations associated with COVID-19 range from mild to severe, including impaired consciousness, acute cerebrovascular disease, and seizures**.** In addition, the clinical manifestations observed were related to intracranial pressure (Michael *et al.*, 2018). This study showed four patients with complaints of headache, where 2 had seizures, and one had general tonic-clonic type with post-ictal confusion, while one other demonstrated complex partial type. Moreover, only one patient respectively experienced bilateral papilledema, mental status alteration, while 2 presented with global aphasia, none showed signs of paralysis, and there was decreased consciousness in 4 individuals. Furthermore, the incidence of visual disturbances and eye movement were observed in 2 patients, 2 experienced myalgia, anosmia was recorded in one, dysgeusia in one, coughing in 3, shortness of breath in 2, rapid and shallow breathing in 1, gastrointestinal complaints, including diarrhea, vomiting, abdominal pain in 2, fever in 3. Meanwhile, one patient demonstrated bilateral VI and VII nerve pareses, and only one experienced upward gaze palsy. According to literature, the most frequent symptom of CVT is headache (nearly 90%), then seizures (39.3%); paresis (37.2%); papilledema (28.3%); altered mental state (22%), aphasia (19.1%), fainting or coma (13.9%), diplopia (13.5%), and visual disturbances (13.2%). However, headaches result from venous distension, local inflammation, or blood vessel leakage, which consequently irritates the dural. The incidence of Todd paralysis occurs in about 54% of patients with cases of seizures (Hernando *et al.*, 2013)**.**

The CVT diagnosis is performed by laboratory and neuroimaging examinations, where frequent findings show an increase in D-dimers and fibrinogen, alongside prolonged blood clotting time, and moderate thrombocytopenia. This disorder is common in patients with coagulopathy resulting from COVID-19. Moreover, hypercoagulation effects encompass the presence of microvascular platelet-rich thrombotic in small vascular vessels of the lung (Hernando *et al.*, 2013). And five of the eight patients of this study (5/8) had increased D-dimer.

Furthermore, Magnetic resonance venography (MRV) and CT-scan venography (CVT) are options for CVT before invasive examinations (angiography and direct cerebral venography) are performed, especially when the results are inconclusive or on instances where endovascular measures are required (Hernando *et al.*, 2013). Meanwhile, all neuroimaging reports showed the presence of venous thrombosis in various areas. The manifestation mechanisms include the occurrence of 1) cerebral vein occlusion, which result in inflow obstruction, venous congestion, consequently leading to increased capillary hydrostatic pressure, and oedema. The histological findings highlight the potential for dilatation and dilation of the veins, oedema, and ischemic neuronal damage, petechial haemorrhage to transform into a haemorrhage. 2) Venous sinus occlusion are often ischemia, and propagates infarction through intracranial emptying, changes in CSF absorption and increased intracranial pressure. This cascade of events eventually prompts venous congestion, and results in ischemia alongside infarction. Based on MRV and CVT, the locations of CVT were identified, including the Galen vein and internal cerebral vein, hypertension. Furthermore, there is an increase in venous pressure, estimated to instigate delayed venous Rosenthal's right basal vein, sigmoid sinus, superior and inferior sagittal sinuses, transverse and straight sinuses, and petechial haemorrhage. In addition, the predominant position includes the transverse sinus followed by the sigmoid sinus. Moreover, CT scan showed areas of generalized or localized hyperdensity in almost 40%. This is estimated to indicate haemorrhagic infarction, which potentially causes intracranial haemorrhage, as observed in the subarachnoid. The exact mechanism of SAH (subarachnoid haemorrhage) in patients with CVT is currently unknown, although the possible instigator includes local inflammatory responses, projected to increase vascular permeability, and consequently allow for blood extravasation to the subarachnoid space. Furthermore, venous parenchymal haemorrhagic infarction is a potential complication of CVT, characterized by the tendency to rupture into the subarachnoid space. The predilection of CVT include transverse sinus 86%, superior sagittal sinus 62%, transverse sinus 18%, cortical vein 17%, jugular vein 12%, Galen and internal cerebral vein 11% (Hernando *et al.*, 2013).

The large variety of clinical manifestations in CVT leads to difficulties during diagnosis, hence neuroimaging is necessary on instances of clinical suspicion. In addition, magnetic resonance venography (MRV) and CT-scan venography (CVT) are suitable options for preliminary examinations prior to invasive checks (angiography and direct cerebral venography). These further assessments are performed when the primary evaluation is not conclusive, or when endovascular measures are required (Hernando *et al*, 2013).

The management of CVT cases is achieved through the simultaneous cerebral venous drainage with LMWH (anticoagulant), anticonvulsant, and decongestant drugs (Hernando *et al.*, 2013), (Virendra *et al.*, 2014). Furthermore, proper diagnosis and immediate cause determination is expected to reduce the incidence of complications (Michael K *et al.*, 2018). The therapy adopted include external ventricular drain (EVD) and heparin drip in 2 patients, thrombectomy in 1 patient, UFH and NOAC (edoxaban) in 1 patient, heparin drip, enoxaparin and acetazolamide to another, while one patient was administered anticoagulant, Levetiracetam, hydroxychloroquine, and Co- amoxiclav.

Five (50%) of the eight patients from the case reports included in this systematic review reportedly died. In addition, systemic or CNS infections were also observed, and there was also a decline in the use of heparin therapy, while the craniectomy approach was more commonly associated with the poor outcomes.

There are few case reports regarding CVT on COVID-19, and the literature explaining the relationship between CVT and COVID-19 is still limited. It is a limitation in this study, and further research is expected to review more cases and a more in-depth pathophysiological explanation.

5. Conclusion

CVT cases in COVID-19 were predominant amongst young adults and without comorbidities (cryptogenic), especially for males. The most common symptoms include headache, and increased D-Dimer. Moreover, all neuroimaging results showed CVT, and the treatment involved the administration of EVD plus anticoagulants. The results showed 50% death.

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