Cerebral Venous Sinus Thrombosis in the COVID-19 Pandemic

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Abstract

Background

Recent studies have noted concern for increased thromboembolic events in the setting of Coronavirus Disease 2019 (COVID-19). Cerebral venous sinus thrombosis (CVST) is a form of thromboembolism that has been observed as a neuro-ophthalmologic complication of COVID-19.

Methods

Review of scientific literature.

Results

In this article, we report an overview of CVST epidemiology, clinical presentation, diagnostics, disease pathophysiology, and management in the setting of COVID-19.

Conclusion

CVST is an uncommon thromboembolic event with variable phenotypes and multiple etiologies. Neurologic complications can be severe, including significant visual deficits and death. Current observations suggest that the risk of CVST may be profoundly impacted by this novel COVID-19 pandemic, thus prompting increased attention to disease presentation, pathogenesis, and management.
Introduction:

Stroke is the fifth leading cause of mortality in the United States affecting 795,000 Americans yearly (1). Cerebral venous sinus thrombosis (CVST) is a complex venous thromboembolic (VTE) phenomenon with variable clinical presentation, many etiologies, and multiple potential complications including stroke and visual loss. While overall incidence and mortality is low, patients with CVST can have significant neuro-ophthalmic disability (2–4). This study provides an overview of CVST with a focus on neuro-ophthalmic complications and highlights the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on CVST given the significant concern for associated increase in thromboembolic events.

Epidemiology

CVST is a rare form of VTE with annual incidence historically noted to be approximately 3 to 4 per million in adults and approximately 7 per million in children (5). More recently, with the advent of advanced imaging techniques combined with overall increased awareness, CVST has been recognized with increasing frequency, with newer studies reporting incidence of up to 15 per million (2,6). Interestingly, these studies have noted up to a three-fold increased incidence in women compared to men, an imbalance likely due to CVST risk factors such as pregnancy, post-partum state, and oral contraceptive use (5,7,8). The median age of patients ranges from 37 to 49 years, with a lower median age in women. This number fluctuates depending on the population studied, but despite this variability, the median age is significantly lower than for arterial strokes (7,8).
CVST is an uncommon mechanism for ischemic stroke with a prevalence of 0.5% and mortality of 4% in pre-COVID-19 pandemic studies (2,3,9). The effect of COVID-19 on both mortality and incidences of isolated CVST and CVST-related stroke has yet to be determined. However, preliminary review of cases within our system indicates a decrease in absolute number of admissions for CVST but an increase in mortality among stroke patients with CVST.

Clinical Presentation

The clinical presentation of CVST is variable, which can create a diagnostic challenge. The median time from symptom onset to diagnosis is approximately 7 days, with women seeking care sooner than men (7,10). Symptoms depend on location and extent of occlusion, sufficiency of collateral venous drainage, mode of onset, patient age, and underlying risk factors (11,12). Clinical features of intracranial hypertension arise when drainage of collateral vessels is sufficient, whereas symptoms related to infarction tend to occur in the setting of venous congestion (12–14). Headache is the most common symptom, present in nearly 90% of patients, and is an isolated finding in 25% of patients, many of whom have associated papilledema on funduscopic examination. Patients older than 50 are more likely to have infarction (10). Other symptoms include altered consciousness, nausea and vomiting, seizures, cranial nerve abnormalities, aphasia, paresis, and paresthesias (7,10).

Visual deficits may be a result of papilledema secondary to raised intracranial pressure (ICP), direct ischemic injury of intracranial visual pathways, and/or direct injury to cranial nerves responsible for ocular motility and pupillary function (15,16). According to the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), visual findings included
papilledema (28%), vision loss (13%), and diplopia (13%), often from sixth cranial nerve palsy (7). Papilledema was noted in 85% of patients with acute (less than 48 hours) and subacute onset (48 hours to 1 month), and in all patients with chronic onset (greater than 1 month). Among those with chronic onset, 65% had visual disturbances secondary to papilledema and post-papilledema optic atrophy (7,10–12).

**Diagnostics**

As clinical presentation is variable, urgent neuroimaging is encouraged if there is suspicion of CVST. Computed tomography (CT) of the head without and with contrast is recommended for initial assessment as it can detect some abnormalities related to CVST as described below (3,12). However, 10-30% of head CTs are normal in the workup for CVST (17,18). Magnetic Resonance Imaging (MRI) in combination with Magnetic Resonance Venography (MRV) of the head has the highest sensitivity and specificity in the diagnosis of CVST (10). Although Digital Subtraction Angiography (DSA) has historically been the gold standard, it has now been replaced by MRI in combination with MRV (19). DSA remains beneficial as it offers a better understanding of the dynamics of the venous system and is reserved for patients with inconclusive neuroimaging studies or if an interventional therapy is being considered (19).

Computed Tomography Venography (CTV) is another diagnostic modality, with evidence suggesting it may be superior to MRV in evaluation of the inferior sagittal sinus, nondominant transverse sinus, and small cortical veins (19).

There are direct and indirect signs of CVST on imaging. Direct signs, present in only a third of the cases, include visualization of the thrombus (dense triangle sign, dense vessel sign, or cord
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sign), a contrast filling defect (empty delta sign), or lack of flow signal (18,19). Indirect signs include venous edema, infarction, parenchymal hemorrhage, or subarachnoid hemorrhage (Figure 1 depicts some of these classic direct and indirect findings) (19). The most common site of occlusion is the superior sagittal sinus (62%), followed by the left lateral (45%) and right lateral sinuses (41%) (7). More than 50% of patients have multiple sinuses involved (10). Infarct is present on imaging in approximately 47% of patients, with hemorrhagic infarct occurring in 20-30% (7,10). Infarcts occur more often in the left hemisphere and rarely involve the posterior fossa (7).

Etiology

Large scale studies have identified several key conditions frequently associated with CVST (2,6–8,10). All of these are classically linked to Virchow’s triad of thrombogenesis: hypercoagulability, hemostasis, and vessel wall injury (20). As such, the most commonly identified risk factors are acquired and congenital thrombophilia (3).

The aforementioned increased incidence among women is due to acquired thrombophilic risk factors including pregnancy, post-partum state, oral contraceptive use, and hormone replacement therapy (8,10). In the ISCVT, 65% of women had these gender-specific risk factors, with 50% of female patients having more than one thrombotic risk factor. Prognosis was better among this cohort, possibly due to younger age and regular check-ups during pregnancy or while on contraceptives (7,8).
Acquired risk factors such as antiphospholipid antibodies, malignancy, arteriovenous malformations, and mechanical head injury are also frequently associated. The most common risk factor in developed countries is congenital thrombophilia, including inherited diseases such as factor V Leiden, prothrombin G20210A mutation, and deficiency in protein C, protein S, and anti-thrombin III (3,7,21). All these conditions have been identified in varying proportions in patients with CVST (10,22,23).

Active or recent infection is another common acquired risk factor. Interestingly, the first report of thrombosis from the 19th century led to a long-standing belief of a direct relationship between CVST and infections (9,24). Current studies reveal that infections account for approximately 10% of adult cases with CVST, especially in developing countries (7,10). These include central nervous system infections, notably, abscess, empyema, and meningitis, as well as local parameningeal infections such as mastoiditis, sinusitis, otitis, facial cellulitis, tonsillitis, and osteomyelitis (3,5,12). Endocarditis, tuberculosis, measles, herpes, human immunodeficiency virus, cytomegalovirus, malaria, aspergillus, and cryptococcus are systemic infections that have been described as well (12). In addition to infections, there is also increased thrombotic risk related to comorbid inflammatory disorders such as Behçet disease, granulomatosis with polyangiitis, sarcoidosis, and systemic lupus erythematosus (4,5,10).

**Therapeutics**

Clinical stabilization is key in this population as patients may present with intracerebral hemorrhage, cerebral edema, elevated ICP with increased risk of herniation, alteration in level of consciousness, and respiratory compromise. In some cases, intensive care unit admission with
administration of hyperosmolar therapies and hyperventilation may be warranted. Additional emergent surgical interventions such as thrombolysis/thrombectomy and decompressive craniectomy (DC) may be necessary if medical management were to fail (3,12,25). Studies assessing safety and efficacy of endovascular treatment have been limited by small number of patients, publication bias, and lack of blinding (26–29). A recent randomized controlled trial revealed that endovascular treatment did not show improvement over standard care. This study was stopped short for futility and was limited in number of patients enrolled (29). Additional studies implementing advanced venous techniques as they are developed may offer better results. Currently, there are no formal guidelines on endovascular treatment for CVST. Although the quality of evidence for DC has also been poor, DC is recommended for patients with acute CVST complicated by parenchymal lesions and impending herniation (25).

In non-emergent cases, early initiation of anticoagulation is a mainstay of treatment of CVST. The use of anticoagulation in CVST has been controversial, largely owing to the presence of venous infarcts with hemorrhagic complications in up to 40% of cases. Studies addressing this question have been few and limited by the low prevalence of CVST. A meta-analysis of two studies noted better prognosis, although not statistically significant, without worsening of hemorrhagic lesions when treated with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) anticoagulation (30–32). UFH may be favored in cases where surgical intervention may require quick anticoagulant reversal. Small studies have shown that LMWH is comparable to UFH, but statistical significance was not achieved since studies were underpowered (33–35). Cumulatively, these studies are meaningful in reinforcing use of early anticoagulation for treatment of CSVT (14).
Recommendations regarding safety and efficacy of direct oral anticoagulant regimens to prevent recurrent CVSTs are currently limited to small observational studies on rivaroxaban and dabigatran (25,36–39). While one larger randomized trial has demonstrated similar safety and efficacy of dabigatran to warfarin, more high-quality studies are necessary (40,41). Given similarities between extracerebral VTEs and CVSTs, it may be reasonable to adopt VTE guidelines with attention to each patient’s thrombotic and bleeding risk profile when considering time-limited anticoagulation for secondary prevention (3).

Additional treatments should be considered for patients with visual compromise secondary to papilledema from elevated ICP. A lumbar puncture (LP) is warranted prior to initiation of anticoagulation in patients with isolated raised ICP, absence of cerebral infarction or hemorrhage, and no other risk factors for herniation. The goal of the LP is to acutely decrease ICP and prevent further visual loss while allowing anticoagulation to have therapeutic effect. Acetazolamide may also be used, although this has a more limited role in the acute management of severe cases of papilledema. Corticosteroids are associated with a worse prognosis in CVST and should be avoided. Surgical management, with either cerebrospinal fluid shunt or optic nerve fenestration, may be needed in severe or refractory cases of elevated ICP and vision loss. A discussion of the benefits and risks of these interventions is needed, particularly in the acute phase, as temporary discontinuation of anticoagulation for any surgical intervention can lead to further thrombus formation. Although ICP normalizes in most cases following treatment of CVST, patients rarely may have chronically elevated ICP and papilledema, requiring long term management (25,42).
Impact of COVID-19 on CVST

Multiple neurologic complications, including encephalopathy, anosmia, ageusia, seizures, strokes, encephalitis, meningitis, and neuropathy have been identified in the setting of COVID-19. Several case-reports have also observed CVST among patients with COVID-19 (9,43–48).

However, reported CVST numbers have been low (first half of the year 2020) as COVID-19 has had a significant impact on the number of overall neurologic admissions. Several studies globally have reported decreased rate of neurologic hospitalizations and admissions. This decrease is thought to be due to increased social distancing, fear of contracting the virus, stay-at-home guidelines, and increased tele-health triaging of clinical problems (49,50). Therefore, while only a handful of CVST cases have been reported to date, it is possible that patients simply have not presented to the hospital because of the aforementioned reasons, particularly if symptoms have been mild. It is also possible that many CVST cases have been underdiagnosed in the pandemic setting. Many patients with COVID-19 presented critically-ill with cardiopulmonary instability often necessitating emergent sedation and mechanical ventilation. This has caused deferral of radiographic studies until clinical stability is maintained, making diagnosis of neurologic disease more difficult (49,51).

While the numbers of reported CVST during the COVID-19 pandemic have been low, the pandemic has helped to further our understanding of CVST pathophysiology and treatments. The role of infections and their association with thrombophilia in CVST is of key interest. Numerous viral infections are associated with coagulopathy, including human immunodeficiency virus,
cytomegalovirus, varicella zoster virus, and Ebola-Marburg virus (52). With regard to respiratory viruses, H1N1 influenza A virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV) have also been shown to have abnormal coagulopathic presentations including disseminated intravascular coagulopathy (DIC), deep vein thromboses, and pulmonary thromboemboli (52,53). While pathophysiology still remains to be elucidated, there is growing consensus that viral infections may lead to profound dysregulation between inherent procoagulant and anticoagulant mechanisms. Suggested mechanisms include endothelial dysfunction, excess inhibition of fibrinolysis, increased blood viscosity, and septic-associated coagulopathy (20,52).

COVID-19, similarly, has been associated with a significant coagulopathy leading to a newly recognized syndrome known as COVID-19-associated coagulopathy involving venous, arterial, and microcirculatory systems (20,54,55). It is known to cause dysregulation of natural anticoagulants resulting in elevated D-Dimer levels and platelet dysfunction with potential hyperactivation via inflammatory cascades (20,48), with whole blood thromboelastograms revealing heightened coagulation parameters (56). While similar to DIC and microangiopathy, factors such as elevated fibrinogen, profoundly elevated D-dimer, and lack of thrombocytopenia have served as key distinguishing markers (20). These findings suggest a potentially strong link between CVST and COVID-19-associated coagulopathy, but supporting evidence is limited and extensive studies are required.

As previously mentioned, the strength of recommendation for anticoagulation in CVST has been challenged given the frequency of concurrent parenchymal hemorrhage on presenting imaging
and the paucity of well-powered studies. The nature of COVID-19-associated coagulopathy bolsters the need for larger randomized trials in this setting. Presently, many experts have recommended therapeutic doses of anticoagulation in COVID-19 when not contraindicated based on anecdotal experience and theoretical physiologic risk; objective scoring criteria as well as case-based recommendations have been proposed to guide clinical decision making (20,57,58). Clinical trials are underway to determine optimal anti-thrombotic regimen.

Conclusion

CVST is an uncommon thromboembolic event with variable phenotypes and multiple etiologies. Neurologic complications can be severe, including significant visual deficits, stroke, and death. Current observations suggest that the risk of CVST may be profoundly impacted by this novel COVID-19 pandemic, thus prompting increased attention to disease presentation, pathogenesis, and management.

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Competing Interests

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FIGURE LEGEND

Figure 1. Common findings of CVST on CT imaging

CT head without contrast revealing cortical vein thrombosis with (a) dense vessel sign and (b) cord sign, as well as (c) dense triangle sign and (d) venous hemorrhage with surrounding edema.