Cerebral vein and dural sinus thrombosis (CVST) is an uncommon cause of stroke, but its delayed diagnosis carries significant morbidity and mortality. Several studies have reported higher incidence of CVST than that previously reported. The clinical presentation of CVST varies and can be atypical. Advancement in neuroimaging modalities has made it possible to make an early diagnosis and initiate management with a wide range of therapeutic options, including direct oral anticoagulants and endovascular treatment. This narrative review summarizes the epidemiology, clinical aspects, diagnosis and management of CVST.

Keywords: Anticoagulation, cerebral vein, direct oral anticoagulants, dural sinus, neuroimaging, thrombosis

INTRODUCTION

Cerebral vein and dural sinus thrombosis (CVST) is an uncommon cause of stroke, with an annual incidence of about 5/million, most commonly affecting those in younger age groups and females.[1‑3] Its clinical manifestations vary, and thus can delay the diagnosis. The most common symptom is headache, followed by focal lobar syndrome, seizures, encephalopathy and cranial nerve palsies.[4] In addition to gender and age, the common risk factors of CVST are thrombophilia, pregnancy, postpartum period, infections and malignancy.[6‑8] In the recent past, computed tomography (CT) and magnetic resonance imaging (MRI) are increasingly being used, which has helped physicians to diagnose CVST more frequently even in patients with atypical presentation.[9] The mainstay of treatment is recanalization of occluded sinus or vein via antithrombotic therapy or endovascular treatment, while adequate symptomatic treatment is required for headache, seizures and intracranial hypertension. Management of the underlying etiology and complications is of utmost importance.[10] Accordingly, this review was conducted to provide an update of the epidemiology, clinical aspects, diagnosis and management of CVST, including discussing the recent European Stroke Organization (ESO) guidelines and the interventional management of such patients, as well as highlights areas of future studies.

For this narrative review, the author searched PubMed, Web of Science and Google Scholar until 2019 using the keywords “cerebral venous sinus thrombosis,” “dural venous sinus thrombosis,” and “diagnosis and management of cerebral venous thrombosis,” and all relevant and current studies were included in the following review.
EPIDEMIOLOGY

Incidence
CVST comprises 0.5%–3% of all strokes. The current epidemiological data on CVST are scarce and vary between countries. Previously, the annual incidence of CVST in adults and children has been estimated as 3–4 and 7/million, respectively. In 1995, a study found that in Riyadh, Saudi Arabia, the annual incidence of CVST was <10/million. However, recently, several countries have reported higher incidence: in Iran, the incidence of CVST has been reported as 12.3–13.5/million, whereas in the Netherlands and South Australia, it has been reported as 13.2 and 15.7/million, respectively. These higher incidences can be due to better methods being used for making a diagnosis, such as neurovascular imaging, as well as due to the fact of females more commonly using hormonal contraceptives, which is a major risk factor for CVST; however, environmental and genetic factors may also be the contributing factors and should be investigated.

Gender and age
Although few studies have reported no gender-related differences, most studies have shown females to be more frequently affected by CVST than males. A recent systematic analysis validated the female preponderance by demonstrating that the proportion of female patients increased from 54.8% in 1966 to 81–69.8% in 2001–14, which could be explained by more frequent use of oral contraceptives (OCs) by females in the recent past. In terms of age, in 2004, Ferro et al. reported the median age of CVST diagnosis as 37 years. In two other studies, the median age was found to be 49 years (range: 40–61 years) and 30 years (range: 6–76 years). Notably, the age of CVST patients is lower than that of patients with arterial strokes.

CLINICAL MANIFESTATIONS

The clinical manifestations of CVST are diverse and depend on the location of thrombus, duration of illness and the associated brain parenchymal changes. Broadly, it can be categorized into the following four major syndromes: (1) intracranial hypertension, (2) focal cerebral dysfunction, (3) encephalopathy and (4) seizures with or without focal neurological deficits (FNDs).

Headache
Headache is the most common symptom, affecting about 70%–90% of CVST patients. Headache can be explained by the stretching of nerve fibers in vessel wall due to increased intracranial pressure (ICP), the release of pro-inflammatory mediators from the clot and/or subarachnoid hemorrhage (SAH).

Isolated headache is reported in up to 25%–40% of CVST patients. Usually, the headache is diffuse, but, sometimes, may mimic migraine and thunderclap/cluster headaches. If caused by increased ICP, headaches can be associated with transient visual impairment or papilledema. The presence of seizures or other FNDs along with headache may suggest an underlying venous infarction. In some cases, an increased ICP can occur in isolation and may be mistaken as idiopathic intracranial hypertension. These diversities in headache pose a diagnostic challenge for treating physicians.

Focal neurological deficits
The presence of FNDs may help in the localization of thrombus. FNDs such as hemiparesis, monoparesis, aphasia, visual field defects including cortical blindness, cranial nerve palsies or hemisensory disturbances can present in up to 18%–72% of patients. The most common FNDs are motor deficits (19%–39% of the patients) and aphasia (19%–24% of the patients). Transient ischemic attack has also been noted in few cases.

Solitary or multiple cranial nerves can be involved, which can sometimes be the sole presentation of CVST. The involvement of III, IV, V, VI, VII, VIII, IX, X and XII cranial nerves has been reported. Isolated sixth nerve palsy without intracranial hypertension has been reported with inferior petrosal sinus thrombosis and transverse sinus thrombosis. Isolated trigeminal neuropathy and facial neuropathy have also been reported. In a study by Duman et al., cranial nerve palsies were detected in 11% of patients with CVST.

Visual field defects have been reported in 10.8%–26.5% of patients with CVST. If FNDs are accompanied by headache, the diagnosis may be easier, but when occurring in isolation, the diagnosis may be delayed.

Seizures
Seizures are relatively common in CVST, affecting about 20%–47% of the patients. In nearly half of the cases, seizure remains focal, but can also generalize and even lead to status epilepticus. Seizures are more frequently observed in patients with supratentorial hemorrhagic lesions, FNDs and thrombosis of superior sagittal sinus (SSS) or cortical veins.

Papilledema and altered consciousness
Papilledema is a common feature in CVST, affecting 28%–80% of CVST patients. However, it is rare in patients without headache. In one study, papilledema was
found to be associated with a median admission delay of 13 days after the onset of symptoms.[43]

Altered level of consciousness is a well-reported feature. It was observed in 17.8% and 14% of the patients in the VENOST[39] and ISCVT[51] studies, respectively. de Bruijn et al.[51] found impaired consciousness (Glasgow Coma Scale [GCS] <14) in 39% and coma (GCS <8) in 15% of the cases and reported coma as an independent predictor of poor outcome. It is more frequently observed in patients having deep-venous system thrombosis (DVST);[42] DVST can lead to bilateral thalamic lesions that can manifest as delirium or amnesia.[84]

Less common presentations
Few cases of nonaneurysmal SAH secondary to CVST have been reported.[45] In one study, ten patients were found to have SAH. Localized SAH, particularly when confined to the parasagittal or dorsolateral convexity of the brain, may suggest the underlying CVST.[46] Psychiatric manifestations can sometimes be the only presentation, and diagnosis is difficult in such cases.[47‑49]

ETIOLOGY AND RISK FACTORS
The etiology of CVST is often multifactorial, and thus identifying one risk factor should not limit the physicians from carrying out complete workup to determine other possible factors.[29] In the ISCVT study, 44% of patients were identified as having more than one risk factor.[1] Although >100 causative factors have been described in literature, the etiology of CVST remains unidentified in 13%–20% of the cases.[1,16,50] Table 1 summarizes the key etiologies and risk factors of CVST, with prothrombotic conditions being the leading causes.[91]

Prothrombotic conditions (congenital/acquired)
In a recent study from India, prothrombotic conditions were the cause of CVST in 62.8% of patients.[18] Prothrombotic genetic factors have been recognized to play a pivotal role in the pathogenesis of CVST. Hyperhomocysteinemia is a known risk factor for venous thrombosis, and the role of MTHFR/ C677T mutation has also been studied.[53] In a meta-analysis, six genes with six polymorphisms were identified; of these, factor V Leiden/G1619A and prothrombin/G20210A were found to be significantly associated with the risk of CVST in adults, while MTHFR/C677T was also found to be associated. Polymorphisms in plasminogen activator inhibitor-1, protein Z and Janus kinase-2 did not show any significant association.[53]

Female-specific risk factors
Usage of OCs, pregnancy and peripartum period are the female-specific factors that increase their risk for CVST.[1,51,54] In the ISCVT study, estrogen (in OCs, hormone replacement therapy and pregnancy) was identified as a risk factor in 65% of the females.[1] Women undergoing in vitro fertilization are also at an increased risk of CVST.[55] In addition to OCs, other modes of hormonal contraception such as transdermal patch and vaginal ring are also associated with the increased risk of CVST.[56] In pregnant women, the highest risk has been observed in the third trimester and in the postpartum period.[57]
Infections
Infection is an important cause of CVST, although it has become less prominent over the years. About 8% of the patients in the VENOST study and 20% of those in a study from India had CVST due to infection. Further, low-to-middle-income countries have a higher frequency of this etiology, ranging from 18% to 34% of all CVST cases. In Saudi Arabia, this etiology has been reported to account for 7%–9.9% of CVST cases.

Malignancy and anticancer medications
In the VENOST study, 5.2% of the patients were reported to have malignancy-related CVST. Further, this cause of CVST was found in statistically significantly higher number of patients aged >50 years (P < 0.001), and breast cancer and hematological malignancies were the most common malignancies. Other studies have reported CVST due to malignancy in 2.3%–4.5%, 7.4%, and 9.9% of the patients. In addition to malignancies, treatment with anticancer medications such as L-asparaginase has also been found to be a risk factor of CVST.

Inflammatory bowel diseases
Inflammatory bowel diseases are another well-recognized risk factor for CVST, found in 1.6% of the cases. As compared to Crohn’s disease, ulcerative colitis is more likely to cause CVST, and is more frequent in young women. Ferro et al. found Behçet’s disease to be a rare cause of CVST, accounting for only 1% of the patients. However, in a recent study from Turkey, this etiology accounted for 9.4% of the patients. In Saudi Arabia, there have been vastly different findings: Daif et al. reported that Behçet’s disease was the underlying etiology in 25% of the patients, whereas Algahtani et al. found it to be the cause of CVST in only 1 of the 111 patients (0.9%).

Lifestyle causes
The association between CVST and lifestyle-related factors such as obesity, exercise and smoking has been studied. Smoking has not been found to be significantly associated with CVST. Zaubier et al. found that for females using OCS, being obese and overweight increases the risk for CVST. Interestingly, for females who did not use OCS, there was no such association. Finally, although a case report has described recurrent CVST in relation to marathon training sessions, further studies are required to establish an association between strenuous exercise/physical activity and CVST.

DIAGNOSIS OF CVST
The diagnosis of CVST should be made on clinical ground and supportive imaging studies and should always be considered in patients with the following:

1. New onset of unusual headache
2. Symptoms of FNDs in the absence of known vascular risk factors
3. Intracranial hypertension
4. Evidence of hemorrhagic infarctions on neuroimaging, especially if the infarctions are multiple and not following arterial vascular territories.

Laboratory investigations
Detailed laboratory investigations are important for determining the underlying cause of CVST, and thus initiating appropriate treatments to avoid recurrence. However, routine screening for thrombophilia and malignancy has been found to have no effect on the disease outcome and was accordingly not recommended in the ESO guideline for the diagnosis and management of CVST.

Role of D-Dimer in the diagnosis of CVST
Measuring serum D-dimer levels before neuroimaging is beneficial in patients presenting with headache suggestive of CVST. Kosinski et al. found that D-dimer levels in patients with CVST are positively correlated with the extent of thrombosis and negatively correlated with the duration of symptoms. However, D-dimer measurement is not recommended in patients presenting with isolated headache and when the duration of symptoms is >1 week, as these are associated with false-negative results.

Neuroradiological investigations
CT scanning, CT venography (CTV), MRI, magnetic resonance venogram (MRV) and digital subtraction angiography (DSA) are the currently available neuroimaging modalities for the diagnosis of CVST. CTV and MRV provide comparable results in the evaluation of CVST, and are thus the choice of technique depending on the patient’s clinical situation, institutional expertise and resources available.

Computed tomography scanning, venography and perfusion imaging
CT scan of the brain is often the first-utilized imaging technique in an emergency setting. It helps to rule out other causes such as cerebral neoplasm and subdural hematoma and can show parenchymal changes suggestive of CVST. It should be noted that noncontrast CT scan can be normal in 25%–30% of CVST cases.

CVST can be diagnosed on CT by direct and indirect signs. Direct signs can be false-positive results for dehydration, elevated hematocrit and reduced flow. The direct signs of CVST (i.e., seeing thrombus within the involved venous sinus or veins) are string/cord sign on plain CT (seen in cortical veins thrombosis as hyperdense, elongated images);
dense triangle sign (corresponds to thrombus in the posterior part of SSS) and empty delta sign (seen in contrast-enhanced CT scan when there is an intraluminal filling defect due to thrombus surrounded by contrast in SSS).^{[67]} Indirect signs are erosion and changes in mastoid and middle ear in infective lateral venous sinus thrombosis; reduced ventricular size due to increased ICP; obstructive hydrocephalus; hemorrhagic and nonhemorrhagic infarctions; contrast enhancement of falx and tentorium; bilateral thalamic edema; micro-juxtacortical hemorrhages and cerebral convexity SAH.

CTV can confirm the diagnosis of CVST by showing the filling defect, enhancement of venous wall and augmented collateral venous drainage.^[68] A Hounsfield unit of >70 has been found to be highly specific for the diagnosis of acute CVST.^[69] CT and CTV findings of patients with CVST are shown in Figures 1 and 2. Whole-brain CT perfusion imaging can be supportive in the diagnosis of CVST by detecting perfusion abnormalities that correspond to venous rather than arterial territorial infarctions. Mokin et al.^[70] in their study on ten patients with CVST who had whole-brain (320-detector-row) CT perfusion imaging along with CTV, found that all perfusion abnormalities were adjacent to the thrombosed sinuses and were different in pattern from arterial territorial infarctions. CT perfusion imaging was also identified as an important prognostic tool by Gupta et al.^[71] who concluded that it can be utilized to assess the clinical outcome.

**Magnetic resonance imaging/magnetic resonance venogram**

MRI has greater sensitivity in detecting brain parenchymal changes, blood clot, blood flow and petechial hemorrhages.^[72] A study protocol should include diffusion-weighted images (DWIs), fluid-attenuated inversion recovery (FLAIR) images, T1 sequence (with and without contrast), T2 sequence and venography. MRV should include time-of-flight and phase-contrast sequences.^[72] Single-slice phase-contrast angiography can be carried out in <30 s, and has been found to have a high sensitivity and specificity.^[73]

Patterns of venous infarction seen on MRI are different from those of arterial strokes. It can be often bilateral, which helps distinguish CVST from arterial territorial infarcts. Conventional MRI sequences including T1-, T2- and T2*-weighted gradient echo (GRE); susceptibility-weighted images; FLAIR and DWI are more accurate than unenhanced CT scan. For diagnosing CVST, these techniques have an overall sensitivity of 72%–84% and a specificity of 90%–95%.^[74] Contrast-enhanced three-dimensional GRE T1-weighted imaging has a 93% sensitivity and a 100% specificity in diagnosing CVST, and is considered even more accurate than the conventional MRI sequences.^[75]

**Digital subtraction angiography**

In the recent past, the use of invasive angiography as a diagnostic investigation has declined significantly. DSA is used in cases where noninvasive imaging modalities are inconclusive, to exclude dural fistula or when chemical/mechanical endovascular thrombolytic therapy is being considered.

Based on the above descriptions, the following are the summarization of recommendations for selecting diagnostic imaging modalities in cases with CVST:

- MRV and CTV can be used as a reliable alternative to DSA for confirming the diagnosis^[65]
- CTV can be used as a reliable alternative to MRV for confirming the diagnosis^[65]
• A combination of MRI/MRV or CT/CTV studies should be performed in suspected cases.
• DSA is indicated only when the diagnosis cannot be reliably established with noninvasive imaging modalities.

**MANAGEMENT OF CVST**

The mainstay of treatment is stabilizing the patient, initiating anticoagulation therapy and treating the underlying cause when presenting as infection and complications. Highlights from the 2017 ESO recommendations for the management of CVST are summarized in Table 2.

**Anticoagulation**

Although systemic anticoagulation is considered the first-line treatment in the management of CVST, its use is controversial especially in patients likely to have poor outcome and in those with cerebral hemorrhage. However, both the American Heart Association/American Stroke Association (AHA/ASA) and the European Federation of Neurological Societies recommend that anticoagulation therapy should be initiated in CVST patients even if parenchymal hemorrhage is identified.

Selection of anticoagulant is an ongoing debate, but it is recommended to initiate low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) therapy at the earliest. A randomized controlled trial demonstrated that patients receiving LMWH had significantly lower mortality than those receiving UFH. In situations where anticoagulation is contraindicated or the patient continues to deteriorate despite anticoagulation, chemical or mechanical endovascular thrombolytic therapy can be considered. However, strong evidence for recommending endovascular treatment is yet lacking.

Following the acute-phase treatment, long-term anticoagulants such as Vitamin K antagonist (warfarin) should be continued with a target to achieve an international normalized ratio of 2–3. Currently, direct oral anticoagulants (DOACs) are gaining attention as potential therapy in CVST. In the acute-phase treatment, DOACs have been found to be comparable with warfarin in preventing the recurrence of venous thromboembolism. The advantages of DOACs over Vitamin K antagonists are rapid onset of action, fewer drug interactions and relatively predictable pharmacokinetics. Therefore, DOACs can be considered as potential therapeutic option in patients for whom warfarin cannot be considered despite being recommended as a first-line treatment. Although DOACs have not been recommended, off-label use is being practiced by physicians. Currently, three commonly used DOACs in the treatment of CVST are apixaban, rivaroxaban (factor Xa inhibitors) and dabigatran (direct thrombin inhibitor). In a recent study, Covut et al.

**Table 2: Summary of highlights from European Stroke Organization recommendations related to anticoagulation for the management of cerebral vein and dural sinus thrombosis**

| Management consideration | Recommendations |
|--------------------------|----------------|
| Anticoagulation in acute-phase treatment of CVST | Treatment of adult patients with acute CVST with heparin in therapeutic dosage is recommended, including in those with ICH at baseline |
| Type of heparin to be used in acute phase | LMWH instead of UFH is recommended; however, this does not apply to patients with contraindication for LMWH or circumstances where fast reversal of the anticoagulant effect is required |
| Thrombolysis and thrombectomy compared with anticoagulation in acute phase | No recommendations |
|   | Good clinical practice point |
|   | Panel did not suggest thrombolysis in acute CVST patients with a pretreatment low risk of poor outcome |
| Duration of anticoagulation therapy | Oral anticoagulants (Vitamin K antagonists) for a variable period of 3–12 months after CVST are recommended to prevent the recurrence of CVST and other VTE |
|   | Good clinical practice point |
|   | Patients with recurrent VTE or prothrombotic condition may need permanent anticoagulation |
| Use of new direct oral anticoagulants such as factor Xa or thrombin inhibitors | Use of new DOACs is not recommended, especially in acute phase |
| Use of AEDs | AEDs in patients with CVST are recommended to prevent early recurrent seizures with supratentorial lesions and seizures. However, the panel did not give any recommendations to prevent using AEDs to prevent remote post-CVST seizures |
| Treatment of CVST in pregnant and puerperal women | Treatment with subcutaneous LMWH in patients with acute CVT is recommended |
| Using contraceptives after CVST | Women in childbearing age group with a prior history of CVST should be told about the risks of combined hormonal contraception and given advice against its use |
| Prophylactic use of antithrombotic drugs in pregnant women with a prior history of CVST | Prophylactic use of subcutaneously LMWH is recommended for women with a prior history of CVST during pregnancy/puerperium having no contraindication for prophylaxis or indication for anticoagulation in therapeutic dosage |

AEDs – Anti-epileptic drugs; CVST – Cerebral vein and dural sinus thrombosis; LMWH – Low-molecular-weight heparin; UFH – Unfractionated heparin; VTE – Venous thromboembolism; DOACs – Direct oral anticoagulants; CVT – Cerebral vein thrombosis; ICH – Intracranial hemorrhage

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found that none of the nine CVST patients managed with apixaban and rivaroxaban developed any serious bleeding or thromboembolic event in the median follow-up of 12 months. Apixaban was also found to be safe and an effective alternative to warfarin in another small case series. Another factor Xa inhibitor that has been reported to improve flow in two patients with deep CVST is edoxaban. It should be noted that although studies to date are suggestive of DOACs being safe and effective, large-scale studies are required to provide strong evidence for its use as first-line therapy.

Thrombolysis
Several case series have reported the therapeutic effect of systemic thrombolysis in managing CVST. In 2014, Viegas et al., in their systematic review of 16 reports where a total of 26 patients received systemic thrombolysis as a treatment for acute CVST, it was found that 88% of the patients became independent, but there were two deaths due to intracranial hemorrhage. Nonetheless, several studies have found the use of various thrombolytics to have good-to-excellent clinical outcome. However, further studies are required to determine if systemic thrombolysis can be used in the place of anticoagulants as first-line treatment for patients with CVST.

Neurointerventional procedures
Neurointerventional procedures in the management of CVST are considered in patients who have clinical deterioration despite receiving proper anticoagulation therapy or in whom anticoagulation therapy is contraindicated, such as thrombocytopenia, bleeding disorders or recent major hemorrhages. Various endovascular treatment methods available are pharmacological thrombolysis, direct aspiration thrombectomy, stent-retriever thrombectomy, balloon thrombectomy, balloon angioplasty and stenting and AngioJet. Although according to the AHA/ASA, there is lack of sufficient evidence to support systemic and endovascular thrombolysis in CVST, these therapeutic options may be considered in expert centers. Najjar et al reported successful recanalization in two patients with extensive CVST using suction thrombectomy technique. Currently, there is no evidence for recommending any endovascular procedure over another, and thus different approaches can be used.

Decompressive hemicraniectomy
Nearly 5% of cases with CVST can have a malignant course with signs of high ICP and transtentorial herniation. In such cases, a decompressive surgery can be a lifesaving procedure that allows a better functional outcome and improves survival rate.

CONCLUSION
The diagnosis of CVST is based on clinical presentation and confirmed by neuroimaging. Presence of direct and indirect radiological signs on CT scan can help make a diagnosis of CVST in emergency settings. Further, CTV and MRV have comparable efficacy. Anticoagulation is the mainstay of treatment. In addition, the use of DOACs and endovascular treatment has shown therapeutic potential; however, large-scale randomized controlled trial data are required before their use is widely recommended. Currently, A clinical trial comparing efficacy and safety of dabigatran etexilate with warfarin in patients with cerebral venous and dural sinus thrombosis (RE-SPECT CVT) and the benefit of EXtending oral anticoAGulation treatment after acute cerebral vein thrombosis trial are ongoing trials that would likely provide clearer evidence regarding the use of non-vitamin K antagonist oral anticoagulants and thrombectomy in patients with CVST. Finally, future studies are also needed to clarify if systemic thrombolysis can be an alternative for anticoagulation therapy as the mainstay of treatment.

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