An Update on Diagnosis and Treatment of Cerebral Venous Thrombosis in Adults: A Narrative Review

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ABSTRACT

Background and Aim: Cerebral venous thrombosis (CVT) are a relatively common disorder of the cerebral venous system accounting for less than 1% of all strokes with a higher prevalence in Iran. Despite the considerable advances in recent years, the diagnosis and treatment of CVT is still challenging predominantly in the emergency setting. Therefore, the present study sought to provide an update on the diagnosis and treatment of CVT.

Materials and Methods: PubMed, Web of Science, Google Scholar, Scopus, Elsevier, and Iranian domestic scientific databases were searched within January 1, 2000, to July 1, 2020. In all the electronic databases, the keywords (in the title/abstract) of “cerebral vein thrombosis” OR “CVT” OR “Cerebral venous sinus thrombosis” OR “CVST” AND “risk factor”, “diagnosis”, “treatment”, and “prognosis” were searched. The unrelated articles, studies not concerning humans or pediatric population, and case reports were excluded from the study. In addition, the articles related to CVT in association with coronavirus disease 2019 were excluded.

Results: According to the findings of the present study, CVT can present with a multitude of signs and symptoms, making it difficult to distinguish from other neurological conditions. While the diagnosis is typically based on brain magnetic resonance imaging and magnetic resonance venography, there is evidence suggesting that the plain computed tomography markers with an attenuation value of > 60.4 Hounsfield unit (HU) and Hounsfield-hematocrit (H: H) ratio of > 1.42 are specific enough to make a definite diagnosis. In terms of therapeutic aspects, although warfarin is still the mainstay of treatment, there is increasing interest toward new oral anticoagulants with promising results in both thrombus recanalization and excellent functional recovery. Balloon angioplasty and mechanical thrombectomy might also be considered in severely progressive cases without response to conventional treatments. It is worth mentioning that even for those achieving favorable outcomes, CVT can remain a disabling condition leading to at least neuropsychiatric complaints.

Conclusion: CVT is a rare and important cause of stroke accounting for less than 1% of all strokes mainly affecting young females. With regard to the rarity of the disease and novelty of the therapeutic approaches, there is a long way to fully identify the best diagnostic and therapeutic approaches to the disease.

How to cite this paper

Introduction

Cerebrovascular accident (CVA) is a syndrome characterized by the acute onset of neurological defects as a result of impaired cerebral blood flow. According to the World Health Organization, CVA is known as a rapidly progressive neurological localized or diffuse disorder lasting for more than 24 hours (1-5).

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Cerebral venous thrombosis (CVT) is a rare type of CVA that is caused by the development of blood clots in venous sinuses responsible for draining the blood from the brain. Intravenous thrombosis could be caused by an imbalance between coagulation and fibrinolysis. The three main mechanisms of this imbalance include the change in normal blood flow,
damage to the vessel wall, and changes in blood components (i.e., overcoagulation) (6).

Although CVT appears to account for less than 1% of cerebrovascular diseases (7), the prompt and accurate diagnosis of the disease is essential as delayed recognition and treatment may lead to permanent disability or even death (8).

On the other hand, the incidence of CVT has increased over the past few years due to the advancement of imaging modalities to detect the thrombosis in early stages of the disease. However, the diagnosis and treatment of the disease is still challenging. Interestingly, there is evidence suggesting a higher incidence of CVT in Iran (9-11).

With this background in mind, the present study aimed to provide a review of the clinical symptoms, diagnosis, and treatment of CVT for the development of more comprehensive approaches to optimal management.

**Materials and Methods**

In this review, the used keywords included “cerebral vein thrombosis” OR “CVT” OR “Cerebral venous sinus thrombosis” OR “CVST” AND “risk factor”, “diagnosis”, “treatment”, and “prognosis”. The international scientific databases, such as PubMed, Web of Science, Google Scholar, Scopus, and Elsevier, and Iranian domestic scientific databases (including Barakatons, Academic Jihad Database, Iranian Medical Library [Medlib], Magiran Database, and Civilica) were searched within January 1, 2000, to July 1, 2020.

The reference lists of the articles identified by the research strategy were screened and included those considered relevant according to the title, abstract, and full text. Accordingly, a total of 85 scientific sources published in English were collected. The unrelated articles, studies not concerning humans or pediatric population, and case reports were excluded from the study. In addition, the articles related to CVT in association with coronavirus disease 2019 infection were excluded from the present review.

**Results**

**Epidemiology**

CVT is caused by the development of blood clots in venous sinuses. The most common sinuses involved are superior sagittal sinus and transverse sinus accounting for 70% and 60.5% of the cases, respectively. Cavernous sinus thrombosis occurs in only 5% of the patients with high mortality and morbidity (12,13).

The incidence of CVT in developing countries is not completely clear, and most of the subjects were identified based on autopsy cases. It is a very rare disease with an average of 1.3 cases per 100,000 people per year which can occur at any age from infancy to adulthood; nevertheless, most reports are among women of reproductive age as the frequency of peripartum and postpartum CVT is estimated to be 12 cases per 100,000 deliveries in pregnant women, which is only slightly lower than that of peripartum and postpartum arterial stroke (14–16).

There is evidence revealing, a higher incidence of CVT is evident in Iran which might be attributed to the differences in the profiles of risk factors in comparison to that reported for European countries (9,10).

CVT is a multifactorial disease with at least one risk factor implicated in 85% of affected adults. The main predisposing factors are prothrombotic conditions induced by hormonal causes (e.g., pregnancy, postpartum period, contraceptive pills, use of androgens, and abortion), coagulopathies (e.g., hyperhomocysteinemia), coagulant protein deficiency (e.g., factor V Leiden mutation, antithrombin, protein C and S deficiency), pyridoxine and cobalamin deficiency, and malignancies (e.g., adenocarcinoma, pancreas, lung, breast, lymphoma, leukemia, and metastasis) (17–19).

Less common causes of CVT are trauma, drugs, local infection mainly in para-meningeal locations, dehydration, systemic diseases (e.g., nephrotic syndrome), vasculitis (e.g., Polyarteritis nodosa, systemic lupus erythematosus, anti-phospholipid antibody syndrome, inflammatory bowel disease) and hematologic diseases (e.g., iron deficiency anemia and paroxysmal nocturnal hemoglobinuria) (20–23).

A higher incidence of CVT in Iran might be attributed to the higher frequency of oral contraceptive consumption, especially in Ramadan (i.e., a religious month). It seems that religious and cultural factors have a great impact on the pattern of oral contraceptive consumption as Muslim women tend to use more oral contraceptives during Ramadan or Hajj ceremony (24).

During Ramadan fasting, the serum concentration of oral contraceptives will increase due to prolonged dehydration predisposing young women to develop CVT (25).

In a study carried out by Sasannejad et al., a five-fold increase in the incidence of CVT was observed in Ramadan in the absence of detectable risk factors other than the use of oral contraceptives (26).

In another study conducted by Khomand et al., a four-fold increase in the incidence of CVT was demonstrated in Ramadan in comparison to that reported for other months of the year (27).

**Clinical Presentation**

CVT can present with a multitude of signs and
symptoms, making it difficult to distinguish from other neurological conditions. The symptoms vary from subacute headache with or without the signs of intracranial hypertension (e.g., nausea, vomiting, diplopia, and blurred vision) to focal sensory and motor deficits, aphasia, visual impairment, seizures, behavioral disorders, loss of consciousness, and even coma in case of bilateral deep vein thrombosis occurring in approximately 16% of the patients or significant hemorrhagic infarcts (28–35).

Additionally, atypical presentations, such as neurogenic fever, have been reported (31).

The headache of CVT is typically described as diffuse and progressive headache. A minority of patients may present with thunderclap headache similar to subarachnoid hemorrhage or migrainous type of headache. Isolated headache without focal neurologic deficit and papilledema occurs in up to 25% of patients posing a considerable diagnostic challenge (33).

There are important features contributing to distinguish CVT from other cerebrovascular diseases. Firstly, the symptoms usually develop in a subacute manner. Secondly, bilateral brain involvement is not uncommon. Finally, a seizure is more frequently occurring in up to 40% of the patients (34).

**Diagnosis**

The diagnosis is typically based on clinical suspicion and confirmatory neuroimaging findings. Cerebral veins and sinuses can be examined using the following different methods (37).

**Brain CT Scan**

Computed tomography (CT) scan is widely used as the first diagnostic test in patients presenting with new-onset focal neurologic deficit. Non-contrast CT is usually normal as the observation of sinus thrombosis itself, which is called dense or filled delta sign observed only in 30% of cases, indication of venous infarction is sometimes hemorrhagic in 30% of patients, or observation of subarachnoid hemorrhage in 0.5–8% of patients. Taking into account all the considerations the detection rate with a non-contrast CT scan is very low (38).

**CT Scan with Contrast**

This method is more sensitive and indicative of the blood clot in the sinus as a focus on central hypodense and peripheral enhancement which is called the empty delta sign, observed in 25% of cases. The empty delta sign might not appear for several days after the onset of symptoms (11).

**CT Venography**

Regarding the accuracy of CTV and MRV, CTV is reported to be more accurate with almost an equivalent diagnostic value of venography. However, for the reasons, such as a skeletal bone artifact arising on the sinuses caused by cranial bone density, use of ionizing radiation, use of iodinated contrast agent (with the possibility of allergies), especially in those with kidney problems, many clinicians prefer performing MRV (39, 40).

Notably, as CTV can rapidly be conducted following a non-contrast brain CT while the patient is still in the CT scanner, it is a viable option in the emergency setting. Nevertheless, it is less sensitive to detect cortical vein thrombosis (41).

More recently, Digge et al. proposed that plain CT is specific enough for the diagnosis of acute CVT, and no confirmatory imaging, such as venography, is needed. However, they concluded that parallel to age clot progression, the sensitivity of CT attenuation would decrease (42).

Similarly, Shayganfar et al. revealed that the attenuation value of $> 60.4$ Hounsfield unit (HU) with 1.42 with 4.9% sensitivity and Hounsfield-hematocrit (H: H) ratio of $> 1.42$ with 94.3% sensitivity calculated based on unenhanced CT could strongly detect CVT in the emergency setting (43).

Moreover, based on a recent meta-analysis, CT was observed to have a reasonable diagnostic accuracy with the pooled sensitivity of 81% (95% CI: 78–84%) and 89% (95% CI: 88–91%) for the diagnosis of CVT regardless of the thrombosis age (44).

**MRI**

MRI is the best noninvasive imaging technique to screen CVT. it is also superior to CT to detect parenchymal edema and infarct (45, 46).

The thrombotic materials show complex properties in signal intensity depending on the time course of thrombosis and imaging sequence as follows.

**Acute Thrombosis**

The stage of its development is within 0-5 days or up to the first week, with 10-30% of patients referring at this stage. As the clot contains doxy hemoglobin observed in isosignal T1-weighted (T1) and hyposignal T2-weighted (T2) imaging, the brain MRI might look absolutely normal at this stage. At this point, gradient echo and susceptibility-weighted imaging could be beneficial as the clot is observed as a black cord. In addition, contrast-enhanced MRI could represent the clot in the form of an empty delta sign (46, 47).

**Subacute Thrombosis**

At this stage, within days 6-15, in which 55% of patients refer, hemoglobin is converted to meth hemoglobin; therefore, it is hypersignal in T1 and T2 images, and it is easily diagnosed. Accordingly,
this stage is the easiest to be diagnosed. The thrombus findings at this stage in contrast-enhanced MRI are similar to those reported for the acute stage (48).

**Chronic Thrombosis**

At this stage, since the second week onward, the clot in the T1 is similar to the isosignal acute phase, and in the T2 it can be isosignal or hypersignal. The residual clot might be enhanced similar to the appearance of normal sinus (i.e., lack of the empty delta sign observed in acute and subacute stages). At this stage, MRV is very helpful because it shows the location of the stenosis and collateral vessel (48, 49) (50).

**MR Venography**

Today, MRV is widely available, and Time of flight (TOF) is a method of MRV currently used in the evaluation and investigation of cerebral sinuses. Using MRI and MRV is one of the accepted methods for the assessment of the anatomy of veins and intracranial sinuses. Two-dimensional-TOF MRV is the most commonly utilized method for the diagnosis of CVT. A recent meta-analysis illustrated that the diagnostic performance of contrast-enhanced MRV was better than that of non-contrast enhanced TOF and phase-contrast MRV (51).

**MRBTI**

Magnetic resonance black-blood thrombus imaging, as a native contrast thrombus MRI technique, has been recently evaluated in the setting of suspected CVT yielding sensitivity of 100% and specificity of 96%, even up to the level of individual venous segments (52).

**Cerebral Angiography**

Cerebral angiography should be used to confirm the diagnosis only when conventional neuroimaging is inconclusive or there is a suspicion of a dural arteriovenous fistula. It is mainly used in rare cases of isolated cortical vein thrombosis without sinus thrombosis and may show indirect signs, such as dilated and tortuous corkscrew collateral veins, as the evidence that there may be thrombosis downstream in the sinuses (16).

Despite all diagnostic methods, CVT is still a challenging medical condition. It is recommended to screen CVT in patients with lobar intracranial hemorrhage of the unclear origin, cerebral infarction crossing typical arterial boundaries, evidence of intracranial hypertension, and headache associated with atypical features (53, 54).

There is also, potential radiologic pitfalls in the diagnosis of CVT among which the main culprits are the anatomic variants of normal venous anatomy, such as sinus atresia, sinus hypoplasia, asymmetric sinus drainage, and normal sinus filling defects related to prominent arachnoid granulation or intrasinus septa (55, 56).

In terms of laboratory evaluation, a complete blood count, coagulation panel, chemistry panel, and inflammatory markers, such as a sedimentation rate and C-reactive protein, should be performed (57).

While D-dimer testing has been well established in ruling out the venous thromboembolism, such as pulmonary embolism and deep vein thrombosis, the usefulness of which is still debatable in CVT, with an unacceptable false-negative rate of up to 26%. Nevertheless, positive D-dimer strengthens the suspicion of CVT in patients with acute headache (23, 58–63).

As previously mentioned, the thrombotic conditions are considered as the leading predisposing factors to develop CVT. However, there is not a global consensus to screen for thrombophilia in all patients. With regard to the European guidelines, in clinical practice, thrombophilia screening may be performed for patients with a high pretest probability of carrying severe thrombophilia, such as a history of personal or familial venous thrombosis, young age, and CVT without a transient or persistent risk factor.

Similarly, it is not recommended to screen for an occult malignancy in all patients (64).

A recent study argued the role of prothrombotic gene variants of deep vein thrombosis, pulmonary embolism, and superficial vein thrombosis development with about 40% of patients showing at least one of the Factor V Leiden, FV H1299R, or Factor II (FII) G20210A variants which were significantly more pronounced in males. Additionally, it seemed that cerebral and retinal vein thromboses were less related to prothrombotic gene variants, and only FII G20210A was relevant, particularly in females (65).

**Treatment**

Treatment should be initiated in case there is a strong clinical suspicion even before the final confirmation of the diagnosis, especially in patients with known risk factors. The treatment of choice is anticoagulants. Both intravenous unfractionated heparin and subcutaneous low-molecular weighted heparin are bridge therapies to oral anticoagulation with a recommendation of vitamin K antagonist (66).

With respect to the European guidelines, there is a weak recommendation of low-molecular weighted heparin over unfractionated heparin (67).
The target goal of the treatment is an international normalized ratio range of 2.0-3.0 within 3-6 and 6-12 months in patients with provoked and unprovoked CVT, respectively (16, 67).

However, in case of severe thrombophilia or recurrent CVT, long-life treatment should be considered (68, 69).

Recently, new oral anticoagulants (NOACs) have been widely regarded as substitutes for warfarin due to their safety and efficacy in recurrent venous thromboembolism. In this regard, there is a growing tendency to use NOACs as potential alternatives to warfarin in CVT (69, 70).

According to the European guideline, NOACs should be avoided at least in the acute phase of CVT (64).

Since 2017, more interest has been growing toward NOACs usage in CVT as the Clinical Trial Comparing Efficacy and Safety of Dabigatran Etxilate with Warfarin in Patients with Cerebral Venous and Dural Sinus Thrombosis (RE-SPECT CVT) revealed the demonstrable efficacy of Dabigatran in comparison to that of warfarin (71).

Furthermore, another open-label comparative cohort of CVT confirmed the higher effectiveness and safety of NOACs (mainly Rivaroxaban and Dabigatran), compared to those reported for warfarin (72).

Furthermore, an ongoing study of Rivaroxaban for Cerebral Venous Thrombosis trail (SECRET) has been designed to evaluate the efficacy of Rivaroxaban in CVT (73).

Additionally, a recent meta-analysis ascertained the comparable efficacy of NOACs in comparison to that reported for warfarin in terms of partial or full thrombus recanalization and excellent functional recovery with a modified Rankin Scale of <2 (74).

Taking into account all the considerations, it is necessary to rigorously evaluate the efficacy of NOACs before they are widely offered as potential alternatives of warfarin in the treatment of CVT.

Another challenge in the treatment is the management of intracranial hypertension. It is strongly recommended to use decompressive surgery for patients with acute CVT and parenchymal lesion with impending herniation, although this is level C evidence (64).

On the other hand, it is not still clarified when and how to restart the use of anticoagulants in patients undergoing decompressive surgery. It is worth mentioning that using steroids, carbonic anhydrase inhibitors, diuretics, and therapeutic lumbar puncture are not recommended for the improvement of the symptoms (64).

It should be noted that no recommendation is made for the use of shunting alone in patients with CVT and superimposed hydrocephalus (64).

Additionally, in advanced cases failing to conventional treatment, endovascular interventions consisted of mainly pharmacologic thrombolysis with balloon angioplasty and mechanical thrombectomy using a Merci device might be considered. Moreover, several single cases and small case series have demonstrated the promising role of stent retrievers and modifications of aspiration thrombectomy catheters in the treatment of CVT (75, 76).

Stam et al. evaluated 20 patients with severe thrombosis using endovascular thrombolysis. In the aforementioned study, 12 patients were comatose, and 14 cases had hemorrhagic infarction. Their findings revealed 12 and 2 subjects with complete remission and neurological deficits, respectively. In addition, six patients died (77).

Similarly, Endrit et al. revealed a favorable outcome of endovascular treatment in three subjects with severe CVT (78) Mokin et al. also investigated 13 patients with a diagnosis of acute CVT undergoing endovascular treatment. Out of 13 subjects, an endovascular intervention was administered in eight patients in case of systemic anticoagulation failure and considered the first-line therapy in five cases. They revealed the complete restoration of blood flow through the affected sinuses at the end of the procedure in 38% of cases. The 3-month follow-up of 11 patients revealed favorable clinical outcomes and mortalities in 45% and 27% of the subjects, respectively indicating the need for improvement in recanalization strategies regarding this disorder (76).

A systematic review of 235 cases in 2017 illustrated that 76% of the patients undergoing endovascular thrombolysis for CVT were reported with mild or no neurological deficits (79).

Another meta-analysis emphasized endovascular therapy in patients with initial intracranial hemorrhage predictive of poorer outcomes (80).

Nevertheless, the main dilemma in endovascular heroic treatment approach includes how to define what considered the failure of conservative treatment and consequently determine the patients who are candidates for endovascular treatment and optimal endovascular approach (81).

Another aspect of the treatment is focused on seizure management. Despite the 40% prevalence of seizure, antiepileptic drugs are used only in case of seizures and supratentorial lesions at presentation (64).

No clinical trials have assessed the optimal timing for anticonvulsant therapy in CVT.

In a study carried out by Öäge Uygun et al. on 23 patients, seizure at the time of the diagnosis of CVT
was reported in 9 subjects recurring in 4 cases. In addition, only two (22%) patients had seizures resistant to antiepileptic drugs over the first month of CVT onset without a significant association with clinical, electroencephalographic, and neuroradiological findings. They showed that seizures were more evident in the postpartum period in those patients with thrombophilia and in case of venous infarcts and/or hemorrhagic transformation (82).

Similarly, in a retrospective, prospective, national, multicenter, and observational study (VENOST) conducted on 1,126 patients, epileptic seizures were mainly presented in the acute phase of the disease with a predilection in females and patients with focal neurologic deficits or altered consciousness, superior sagittal sinus, and cortical vein involvement. Additionally, a seizure was considered a worse prognostic factor in the first month of the disease without a considerable effect thereafter (83).

**Prognosis**

The patients with CVT have overall favorable outcomes. However, approximately 3-15% of the cases would die or depend on self-care. The outcome of patients with CVT varies from complete recovery to persistent neurologic deficits based on the time of diagnosis and treatment initiation. It is worth mentioning that even for those achieving favorable outcomes, CVT can remain a disabling condition. Long-term follow-up studies suggest that up to 60% of these normal young individuals have ongoing neuropsychiatric complaints, headache, and fatigue with one-quarter of them unable to return to work (84,85).

On the other hand, there has been a tendency to reduce the frequency of focal deficits or coma as the manifestations of CVT and decrease in mortality over time. According to prospective studies, the poor prognostic factors include the male gender, age of > 37 years, severity of the neurological features, evidence of intracranial hemorrhage, venous infarct, thrombosis of deep vein structures, underlying cancer, central nervous system infection, and hereditary thrombophilia.

The risk stratification scores might improve to identify the high-risk patients (86,87).

A 10-year retrospective study revealed the negative association of fasting blood glucose (FBG) on admission with the severity of CVT suggesting FBG as a predictor of short-term poor outcome among CVT patients (88).

Another single-center cohort study on 81 patients, brought up cardiac marker, plasma cardiac troponin (cTn) deviation as a poor prognostic factor of CVT (89).

There is limited number of studies suggesting venous recanalization as a surrogate biomarker for functional outcomes in CVT (90).

Another challenge is the necessity for the evaluation of venous recanalization. There is insufficient evidence about the association of recanalization and clinical outcomes in patients with CVT. Although the American Heart Association/American Stroke Association guidelines acknowledge that follow-up neuroimaging is reasonable, its role in therapeutic decision-making has not been discussed (91).

A 2018 systematic review assessing 818 cases of CVT reported venous recanalization in 694 patients (85%). The overall recanalization trended to increase over time, and the main predictors of recanalization were the female gender, younger age, and underlying identified etiology. Additionally, there was a statistical relationship between clinical outcomes and recanalization. However, it is required to collect further data to ascertain the need for recanalization in patients under anticoagulant therapy with a clinical resolution of the symptoms (90).

**Conclusion**

CVT is a rare and important cause of stroke accounting for less than 1% of all strokes mainly affecting young females (6).

The symptoms are associated with the involved intravenous structure, presence of a qualified collateral system, and increased intracranial pressure ranging from headache to focal neurologic deficits, seizure, and coma (21–23,31).

The diagnosis is typically based on clinical suspicion and confirmatory neuroimaging. Angiography is the historical diagnostic standard for CVT, but is rarely used nowadays and replaced by MRI and MRV (11,35,37,38).

Currently, the treatment is based on anticoagulant therapy in which an increasing trend has been toward NOACs. In addition, in severe and potential fatal cases, heroic treatments, such as decompressive surgery and endovascular thrombolysis, might contribute to better prognosis (21,64,66–71).

The risk stratification scores predict the poor prognosis for the identification of high-risk patients (78,79,81).

Overall, with regard to the rarity of the disease and novelty of the therapeutic approaches, there is a long way to fully identify the best diagnostic and therapeutic approaches to the disease.

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Authors’ contributions
SP developed the idea for the position paper and wrote the initial draft of the manuscript, which was fully reviewed and revised by the other author. The complete manuscript was commented on, revised, and approved by all the authors.

Conflicts of interest
The authors declare that there is no conflict of interest.

Ethical considerations
It was ensured that all the authors were actively involved in the process of the present study and will hold themselves jointly and individually responsible for its content.
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