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

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ABSTRACT

Background and Aim: Cerebral venous thrombosis (CVT) a relatively rare form of acute stroke. Despite recent advances, the diagnosis and treatment of CVT is still challenging predominantly in the emergency setting. The present study sought to provide an update on the management 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 treatment aspects, although warfarin is still the mainstay of treatment, there is increasing interest toward new oral anticoagulants with promising role in both thrombus recanalization and 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 with apparent favorable outcome, CVT can remain a disabling condition associated with at least some degrees of neuropsychiatric deficits.

Conclusion: CVT is a rare and important cause of stroke predominantly in female. Given the diversity of the clinical manifestations, it might be under diagnosed leading to remarkable neurological deficit and even death.

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Introduction

Cerebrovascular accident (CVA) is a syndrome characterized by the acute onset of neurological deficit 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).

Cerebral venous thrombosis (CVT) is a rare type of CVA that is caused by development of blood clots in cerebral venous sinuses. Although, the pathophysiology of CVT is not fully understood, the intravenous thrombosis formation is assumed to be related to 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).

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. Notably, there is evidence suggesting a higher incidence of CVT in Iran (9-11). However, the diagnosis and treatment of the disease is still challenging.

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, we used the keywords "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 Barakatkns, 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. 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 development of blood clots in cerebral venous sinuses, of which, superior sagittal sinus. Cavernous sinus thrombosis occurs in only 5% of the patients with high mortality and morbidity (12,13).

The incidence of CVT varies between studies, but it is estimated to be 3-4 cases per million per year. Overall incidence of CVT in Iran is higher compared to European countries which be attributed to the different baseline characteristics of Iranian population (9,10)

It 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).

CVT is a multifactorial disease with at least one risk factor implicated in 85% of affected adults. The main predisposing factors are prothrombotic conditions as acquired prothrombotic conditions (e.g., pregnancy, postpartum period, contraceptive pills, use of androgens, and abortion), inherited coagulopathies (e.g., hyperhomocysteinemia, coagulant protein deficiency as factor V Leiden mutation, anti-thrombin, 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 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 (36).

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).

- **Neuroimaging**

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. In 30% of cases, Non-contrast CT shows direct signs of thrombosis as dense clot sign or cord sign. Indication of venous infarction is also seen in 30% of patients, and subarachnoid hemorrhage is evident in only 0.5-8% of patients (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 magnetic resonance venography (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 MRV (39, 40).

CTV can rapidly be conducted following a non-contrast brain CT while the patient is still in the CT scanner and it can be easily used 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 to enough diagnosis of acute CVT, and no confirmatory imaging, such as venography, is needed. However, parallel to age clot progression, the sensitivity of CT attenuation decrease (42).

Similarly, Shayganfar et al. revealed that the attenuation value of > 60.4 Hounsfield unit (HU) with 71.4% 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 a reasonable diagnostic accuracy with the pooled sensitivity of 81% (95% CI: 78-84%) and 89% (95% CI: 88-91%) to diagnosis of CVT regardless of the thrombosis age (44).

Brian MRI

Magnetic resonance imaging 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 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 to diagnose 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 with a sensitivity of 100% and specificity of 96%, even up to the level of individual venous segments (52).

Cerebral Angiography

Cerebral is used 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).

Diagnostic challenges with neuroimaging modalities

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).

- ***Laboratory investigation***

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).

However, there is not a global consensus to screen 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 diagnosis, especially in patients with known risk factors.

Anticoagulant therapy

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 paid to NOACs usage in CVT as the Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate 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).

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).

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 that reported for warfarin in terms of partial or full thrombus recanalization and excellent functional recovery with a modified Rankin Scale of < 2 (74).

Symptomatic therapy to control intracranial hypertension

Cerebral edema is common in CVT. However, mild edema improves with anticoagulant therapy. In cases of severe intracranial hypertension, as patients with acute CVT and parenchymal lesion with impending herniation, it is strongly recommended to use decompressive surgery with level C evidence (64).

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

No recommendation is made for the use of shunting alone in patients with CVT and superimposed hydrocephalus (64).

Endovascular treatment

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 treatment 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).

Seizure control

Another aspect of the treatment is focused on seizure management. Despite the 40% prevalence of seizure, antiepileptic drugs are given to patients with seizures and supratentorial lesions (64).

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

In a study carried out by *Özge 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 refractory seizures over the first month of CVT without a significant association with clinical, electroencephalographic, and neuroradio-logical findings. They showed that seizures were more frequent in the postpartum period in those 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 as a worse prognostic factor in the first month of the disease without a considerable effect thereafter (83).

Prognosis

Patients with CVT have overall favorable outcomes. However, approximately 3-15% of the cases would die or depend on self-care. Even for those with favorable outcome, 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).

Markers for poor long term prognosis include male gender, age of > 37 years, altered mental status, intracranial hemorrhage, venous infarct, deep vein thrombosis, infectious or malignant etiology, and hereditary thrombophilia (86, 87).

A 10-year retrospective study revealed the negative association between 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) elevation 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).

Furthermore, another challenge is the necessity to evaluate the venous regarding recanalization. There is insufficient evidence regarding 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 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 tended 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 outcome 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 potentially life-threatening cause of stroke (6).

The clinical presentation relies on the involved intravenous structure, presence of a qualified collateral system, and increased intracranial pressure varying from mild headache to focal neurologic deficits, seizure, and coma. The diagnosis is typically based on clinical suspicion and radiologic findings. Angiography is the historical diagnostic standard to diagnose CVT, but it is rarely used nowadays and replaced by MRI and MRV. Currently, the treatment is based on anticoagulant therapy. In potential fetal cases, heroic treatments as decompressive surgery and endovascular thrombolysis, might be considered.

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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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