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Cerebral Venous Thrombosis: an Update

José M. Ferro [1,2] · Diana Aguiar de Sousa [1,2]

Abstract

Purpose of Review The purpose of this update is to summarize the recent advances on the management of cerebral venous thrombosis (CVT).

Recent Findings There is a trend in declining frequency of CVT patients presenting with focal deficits or coma and a decrease in mortality over time. Anemia and obesity were identified as risk factors for CVT. During pregnancy and puerperium, the higher risk of CVT occurs in the first months post-delivery. With appropriate management, 1/3 of comatose CVT patients can have a full recovery.

Summary The management of CVT patients includes treatment of associated conditions, anticoagulation with parenteral heparin, prevention of recurrent seizures, and decompressive neurosurgery in patients with large venous infarcts/hemorrhages with impending herniation. After the acute phase, patients should be anticoagulated for 3–12 months. Results of recently completed randomized controlled trials on endovascular treatment and comparing dabigatran with warfarin will improve the treatment of CVT.

Keywords Cerebral venous thrombosis · Dural sinus thrombosis · Cerebral vein · CT venography · MR venography · MRI · Prognosis · Anticoagulants · Dabigatran · Seizures · Intracranial hypertension · Decompressive surgery · Hemicraniectomy · Thrombolysis · Thrombectomy · Pregnancy

Introduction

Thrombosis of the dural venous sinus or of the cerebral veins (CVT) is a special anatomical location of venous thrombosis [1] and a particular type of stroke, less common and quite distinct from arterial strokes. Contrasting with arterial stroke, CVT (1) is less frequent, (2) affects younger patients with a female predominance, (3) has in general a non-apoplectic onset, (4) rarely presents as a stroke syndrome, (5) has a wider spectrum of clinical presentation syndromes, (6) a more difficult diagnosis, which is often delayed or even missed, (7) has multiple risk factors and associated conditions, (8), most of the vascular risk factors for arterial are not risk factors for CVT, (9) has a different treatment, similar to systemic deep venous thrombosis, consisting mainly of parenteral heparin followed by oral anticoagulation, even in patients with parenchymal bleeding, and measures to reduce increased intracranial pressure, and (10) has a much more favorable outcome [2, 3].

There are very few studies with good quality on the epidemiology of CVT, particularly in low-middle income countries, where CVT incidence appears to be higher, probably reflecting high pregnancy rates and high prevalence of infections and nutritional deficits. In high-income countries, a study conducted in the Netherlands found an overall incidence of 1.32/100000/year and of 2.78/100000/year for women between the ages of 31 and 50 [4]. A retrospective study in Adelaide, Australia, using International Classification of Disease codes for CVT and neuroimaging reports, found an incidence of 1.57/100000/year, with a non-significant higher relative risk (1.18) in females of reproductive age [5]. A systematic review including of 8829 CVT patients, from 74 case series with more than 40 subjects, found an average age of 32.9 years and male to female ratio of 2:3 [6]. This review also showed a clear trend in declining frequency of CVT patients presenting with focal deficits or in coma and a decrease in mortality over time. This declining in mortality can be due

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✉ José M. Ferro
jmferro@medicina.ulisboa.pt

Diana Aguiar de Sousa
dianasousa@campus.ul.pt

[1] Serviço de Neurologia, Department of Neurosciences and Mental Health, Centro Hospitalar Lisboa Norte, Instituto de Medicina Molecular, Lisbon, Portugal

[2] Faculdade de Medicina, Universidade de Lisboa, Avenida Professor Egas Moniz s/n, 1649-035 Lisbon, Portugal

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to better management, and a decrease in septic CVT, but probably is mainly due to the identification of less severe cases by MRI. Over time there was also a shift in sex ratio with an increase in the proportion of women affected, possibly associated with an increase in the use of oral contraceptives [7]. CVT is rare in elderly patients. A recent study confirmed that in older patients, the sex ratio is evenly distributed, cancer is more frequent, and the outcome is worse than in younger CVT patients [8].

Etiology

Conditions associated with CVT can be classified as predisposing (e.g., genetic prothrombotic diseases, antiphospholipid syndrome, cancer…) or precipitant (oral contraceptives, infections, drugs with prothrombotic action…) (Table 1). Most of these associated conditions cannot be named risk factors or causes of CVT, because they do not fulfill the causality principles. Associations were described mostly in case reports or case series and only a few were investigated in case-control studies [9••].

Table 1 Common associated conditions of CVT

Women-specific risk factors
Oral contraceptives
Pregnancy
Puerperium
Hormone replacement therapy
Genetic thrombophilia
Protein S, C and anti-thrombin deficiencies, factor V Leiden, and prothrombin mutations
Acquired prothrombotic diseases
Neoplastic diseases
Myeloproliferative neoplasms
Leukemia
Solid neoplasms
Meningioma
Inflammatory diseases
Antiphospholipid syndrome
Systemic lupus
Inflammatory bowel disease
Nephrotic syndrome
Infections
Head and neck
Ear, mastoid, sinus, nose, face, skull
Systemic
Diagnostic and treatment procedures
Chemotherapy, central venous catheter
Lumbar puncture, neurosurgery
Emerging risk factors
Anemia
Obesity

A multicenter case-control study [10•] compared women under the age of 50 who had suffered a CVT with historical controls to clarify the association between CVT and pregnancy-puerperium. No association was found with pregnancy, while the risk was increased during the post-partum period (adjusted OR 10.6). The risk was highest during the first 6 weeks post-partum (adjusted OR 18.7). This study has several limitations such as the use of historical controls and very few CVT cases during pregnancy and its results cannot be generalized to low-middle income countries. Using the same method, Zuurbier et al. [11] reported an increased risk of CVT in obese women (OR 2.63). In women who used oral contraceptives, overweight and obesity were associated with an increased risk of CVT in a dose-dependent manner. Silvis and co-workers [12•], in a similar study, confirmed that cancer is a strong risk factor for CVT, particularly within the first year of diagnosis and in hematological type of cancer. Risk factors for CVT in patients with leukemia included treatment with asparaginase, high-dose steroid regimens, intrathecal methotrexate injections in acute lymphoblastic leukemia [13–15], and all-transretinoic acid in acute promyelocytic leukemia [16]. Anemia defined accordingly to World Health Organization criteria is also a newly identified risk factor for CVT [17]. Anemia was also associated with unfavorable outcome. Elevated factor VIII collected several months after the acute period was much more frequent in CVT patients than in controls, indicated that it can be a risk factor for CVT [18]. In the VENOST study, conducted in Turkey, Behçet's disease was the cause of CVT in 9.4% of the patients. Most of the patients had a subacute course and an intracranial hypertension syndrome associated with thrombosis of the transverse sinus [19].

Clinical Features

Symptoms and signs of CVT can be grouped in presenting syndromes, the most frequent ones being isolated intracranial hypertension syndrome, focal syndrome, and encephalopathy [20]. Less frequent presentation syndromes are cavernous sinus syndrome or syndromes of multiple palsies of the lower cranial nerves.

In the VENOST study [21•], a large Turkish multicenter retrospective study which collected 1144 patients, onset was acute in 47%, subacute in 34%, and chronic in 19%. Most frequent clinical symptoms and signs were headache (87%), which was isolated in 25%, nausea and vomiting in 28%, seizures in 24%, visual field defects in 27%, other focal neurological deficits in 18%, altered consciousness in 18%, and cranial nerve palsies in 18%.

The clinical presentation of CVT varies according to the age of the patient. In elderly patients, encephalopathy is more frequent, while headache is less often reported [8, 22].

Another factor influencing clinical presentation is the cerebral venous topography of the thrombosis. A systematic review of 116 patients with isolated cortical vein thrombosis [23] confirmed that the most common symptoms/signs of isolated cortical vein thrombosis were headache, seizures, and focal neurological deficits. No patients had papilledema.

A few CVT patients present as non-aneurysmal subarachnoid hemorrhage, either generalized or localized to a single or few cortical sulci of the hemispheric convexity [24, 25] or to the perimesencephalic cisterns [26]. On a retrospective review of 138 patients with CVT [27], subarachnoid hemorrhage in the absence of venous infarct occurred in only 3 patients (2.2%). While CVT patients with generalized subarachnoid hemorrhage present with headache and stiff neck, those with convexity subarachnoid hemorrhage have a more complex symptomatology. In a series of 10 cases of convexity subarachnoid hemorrhage associated with CVT, all were due to superior sagittal sinus thrombosis. All patients had headache, 9 experienced seizures, 4 had papilledema, and only 4 presented meningeal signs [24].

Seizures can be focal or reported as generalized from onset and may evolve to status epilepticus. In a large administrative US database, 16% of hospitalized CVT patients had seizure [28]. Acute symptomatic seizures are more frequent in CVT patients with supratentorial lesions, in particular if hemorrhagic, in those with motor and sensory deficits and in cases with thrombosis of the superior sagittal sinus or cortical veins [29–32]. CVT patients can also present as status epilepticus, or status epilepticus may develop, particularly in patients with severe forms of CVT with supratentorial lesions, especially if multiple and hemorrhagic. Status may be refractory in about 1/6 of the patients, with refractoriness being related to the pretreatment duration of status [33•]. Nevertheless, at 6 months, 84% of CVT patient who had status epilepticus had good recovery. Status was not an independent predictor of poor outcome.

A few patients have a severe presentation as encephalopathy or coma and may need intensive care [34, 35]. These patients have decreased consciousness, altered mental status, bilateral or multifocal signs, and/or seizures or status epilepticus. They usually have multiple sinus occlusion, in particular combining the superior sagittal sinus and the deep cerebral vein system, and show bilateral parenchymal lesions, diffuse brain edema, or a large herniating lesion. In a German multicenter neurocritical unit study of 114 CVT comatose patients, 1/3 recovered fully (mRS 0–1), 10% were severe disabled, and 1/3 died. Clinical deterioration after admission, midline shift, and age predicted poorer outcome [34].

Clinical scores may be useful to predict outcome after CVT [36]. Barboza et al. [37] derived a CVT grading scale (CVT-GS) from a large multicenter Mexican series. The score is composed of parenchymal lesion size > 6 cm (3 points), bilateral Babinski signs (3 points), male sex (2 points), parenchymal hemorrhage (2 points), and level of consciousness (3 points). CVT-GS had an accuracy of 91.6% for prediction of 30-day mortality and 85.3% for mRS > 2 and was superior to CVT risk score [36] derived from the ISCVT cohort (now available as a free App) to predict 30-day mortality. This score does not include associated conditions in the prediction of outcome and needs validation in an independent sample.

Diagnosis

Diagnosing CVT in the emergency setting can be challenging [38•]. Whenever CVT is suspected, urgent neuroimaging is required [39••]. There are still no validated pretest clinical probability scores or laboratory tests that can confidently rule out CVT. Although D-dimer is a potentially useful diagnostic tool before imaging examination, false negatives can occur, particularly in patients with isolated headache or prolonged duration of symptoms (i.e., more than 1 week) [40].

In about one quarter of patients, classic direct signs of CVT may be detected in plain CT, such as the "dense triangle" (clot in the superior sagittal sinus), the "empty delta sign" (non-opacified thrombus surrounded by the collateral veins of the sinus wall after injection of contrast), the "cord sign" (thrombosis of cortical or deep veins) or an increase in attenuation of the occluded sinus [41]. However, these signs are less common in subacute/chronic cases and are not specific. CT venography is a sensitive technique for detection of low flow and demonstration of filling defects in the dural sinus and veins can confirm diagnosis of CVT. This is particularly useful in patients with contra-indication to perform MRI or in centers with limited access to MRI. However, the diagnostic yield of CT venography alone is limited by the common presence of several anatomic variants that may mimic sinus thrombosis (sinus atresia/hypoplasia, asymmetrical sinus drainage, normal sinus filling defects related to prominent arachnoid granulations, or intrasinus septa) and the difficulties in detecting cortical veins thrombosis [23, 42].

Concerning MRI, the signal in T1 and T2 can appear falsely reassuring in the acute phase and diagnosis of isolated cortical vein thrombosis is challenging. Therefore, use of T2*-weighted gradient recalled echo (T2*GRE) or susceptibility weighted imaging (SWI) is recommended to improve diagnostic accuracy, allowing the identification of intraluminal thrombus as a hypointense area [43]. Use of 3D T1-weighted black blood sequences has also shown promising results [44, 45]. MR venography alone has several limitations, particularly in patients with hypoplastic sinus, cortical vein thrombosis, or partial sinus occlusions. Contrast-enhanced MR venography is more sensitive than time-of-flight MR venography, in which artifacts may be produced when there is flow in the plane of image acquisition [46].

Intraarterial angiography should be reserved to cases with inconclusive or contradictory findings in the other imaging modalities, to exclude a dural arteriovenous fistula or when an endovascular therapeutic intervention is planned [42, 47].

Small non-traumatic juxtacortical hemorrhages account for up to one-fourth of intracerebral hemorrhages in patients with CVT and are associated with superior sagittal sinus occlusion. The brush sign (Fig. 1), an abnormally accentuated signal drop of the subependymal and deep medullary veins in paramagnetic-sensitive MR sequences, is occasionally found in CVT, especially in patients with thrombosis of the deep venous system or straight sinus. This sign likely represents increased deoxyhemoglobin and engorgement of the deep veins and is associated with clinical presentation with focal signs, more extensive thrombosis, and ipsilateral parenchymal brain lesion [48].

Treatment

The European Stroke Organisation and the European Academy of Neurology issued a comprehensive guideline for the management of CVT [39••]. The guideline followed the GRADE system, which increases objectivity, decreases bias, and makes the rating of recommendations simpler and clearer. The recommendations are schematized in Table 2.

In the acute phase, all CVT patients should be anticoagulated parenterally with either unfractionated IV heparin or SC low molecular weight heparin (LMWH). LMWH is preferable, unless the patient is clinically unstable, or a lumbar puncture or surgery is planned. A systematic review and meta-analysis confirmed the evidence gathered by the European CVT Guidelines group, by reporting a trend in favor of LMWH in mortality and functional outcomes, with similar rates of systemic bleedings [49]. Observational studies described reassuring low rates of new or enlarging intracranial bleeding in cases of CVT with specific associated conditions (head trauma [50]; head and neck infections [51]) or clinical features (posterior fossa lesions [52]), where anticoagulation could potentially be considered unsafe.

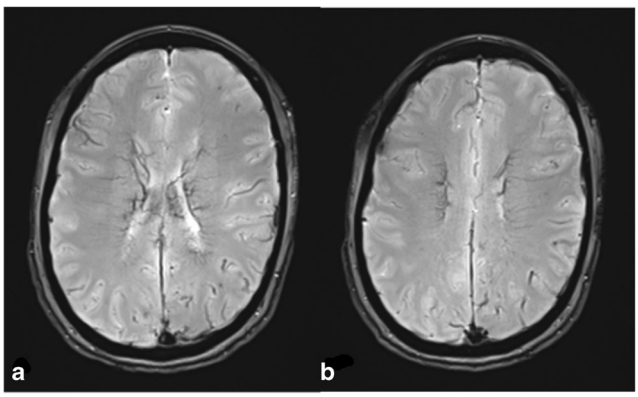

Fig. 1 Brush sign (**a**, **b**, T2*-weighted imaging) in a patient with thrombosis of the superior sagittal sinus, torcula, straight sinus, deep venous system, and left lateral sinus

Patients with large hemispheric lesions, usually hemorrhagic, and impending herniation should be offered decompressive neurosurgery, in general hemicraniectomy. No RCT of decompressive hemicraniectomy was specifically performed in CVT, but such trial is unlikely to be feasible and will be considered by most as unethical. In retrospective series, the vital and functional outcomes of decompressive craniectomy in CVT are much better than in ischemic or hemorrhagic stroke [53•].

Endovascular acute treatment of CVT remains an unproven therapy. The US Guidelines state that endovascular treatment can be considered for patients who are comatose or who deteriorate despite anticoagulation and have no parenchymal lesion with significant mass effect [54, 55]. Due to the very low quality of available evidence, the European guidelines do not make any recommendation and suggest not using endovascular treatment in acute CVT patients with a pretreatment low risk of poor outcome [39••]. A systematic review of case series of more than 3 CVT cases treated with mechanical thrombectomy, 40% of who had encephalopathy of coma, reported a mortality of 14%, with worsening or new intracranial hemorrhage in 9%, complete recanalization in 69%, and complete recovery in 35%. Chemical thrombolysis in conjunction with mechanical thrombectomy did not result in additional harm or benefit, compared with other techniques [56]. However, without a control group, no firm conclusions on the efficacy and safety of thrombectomy can be inferred. Two studies provided important evidence against the use of endovascular thrombectomy or thrombolysis in acute CVT. The randomized controlled trial of thrombolysis or anticoagulation for severe acute CVT (TO-ACT) [57] was terminated prematurely for futility. Of the 67 randomized patients, no difference in clinical outcome was detected between those allocated to anticoagulation and endovascular treatment. In an evaluation of the Nationwide Inpatient Sample 2004–2014, patients receiving endovascular treatment experienced higher mortality (OR 1.96) after adjusting for age and CVT-related complications [58•].

After initial parenteral anticoagulation, oral anticoagulants (vitamin K antagonists) should be used for 3–12 months, or for more prolonged periods in patients with genetic (e.g., protein C, S and antithrombin deficiencies) or acquired (antiphospholip syndrome, active cancer) prothrombotic conditions with high risk of recurrent venous thrombosis. The European Guidelines [39••] recommend against the use of direct oral anticoagulants (factor Xa or thrombin inhibitors) for the treatment of CVT, because of the very low level of available evidence, consisting of small case series without controls. Recently, an exploratory randomized controlled trial (RE-SPECT CVT) comparing the efficacy and safety of dabigatran 150 mg, bid, versus dose-adjusted warfarin (INR 2–3) during

Table 2 Summary of CVT treatment, following the 2017 European Stroke Organization and European Academy of Neurology Guidelines [39••]

Treatment	Recommendation
Heparin in the acute phase	For, strong
Low molecular weight heparin preferable to unfractionated heparin	For, weak
Endovascular treatment	No recommendation
Duration of oral anticoagulation 3–12 months	For, weak
Direct oral anticoagulants	Against, weak
Therapeutic lumbar puncture	No recommendation
Acetazolamide to improve outcome	Against, weak
Acetazolamide to improve headache or visual disturbances	No recommendation
Steroids to improve outcome	Against, weak
Steroids to treat associated Behcet's disease or other inflammatory diseases	For, weak
Shunting to improve outcome in patients with parenchymal lesions with impending herniation	Against, weak
Decompressive surgery to improve outcome in patients with parenchymal lesions with impending herniation	For, strong*
Antiepileptics in patients with acute seizures and supratentorial lesions	For, weak
Antiepileptic drugs in patients with remote seizures	No recommendation
Low molecular weight heparin in CVT during pregnancy or puerperium	For, weak
Not contraindicating further pregnancies	For, weak
Low molecular weight heparin during subsequent pregnancies	For, weak

Strong recommendation, based on moderate (e.g., low-quality randomized control trials (RCT)) or high-quality (e.g., high-quality RCT, meta-analysis of RCTs) information

*Upgraded recommendation, based on balance of benefits and harms, values, and preferences of the patients

Weak recommendation, based on very low (e.g., case series) or low-quality (e.g., case control and cohort studies) evidence

6 months was completed, after allocating 60 CVT patients to each treatment arm. Results are waiting publication [59].

Outcome

Recent large CVT series confirmed that nowadays, acute CVT have low death rates (0 to 2%) [21•, 60]. Pulmonary embolism is a cause of death in acute CVT, but is much less frequent than after deep venous thrombosis of the limbs (1.4% vs. 6.6%, HR 0.26) [61]. In last years, there was interest in the subtle consequences of CVT in patients with apparently full recovery. About 1/3 of CVT patients did not return to paid work. This was more frequent in females and in patients with parenchymal lesions [62]. In CVT patients with bilateral vision 10/10 and normal fundoscopy and visual field tests, optical coherence tomography demonstrated significant axonal loss [63]. Male gender, myeloproliferative neoplasm, factor V Leiden mutation but not persistent venous occlusion were confirmed as risk factors for recurrence of venous thrombotic events after CVT [64, 65, 66•]. In a South-American cohort [66•], recurrence of venous thrombotic events after CVT was lower (1.6/100 patients-years) than in previous studies (~4/100), but the mean age was only 30 years, and most CVT patients were women taking oral contraceptives or pregnant/puerperal, without associated prothrombotic conditions. Therefore, they had a lower risk of further venous thrombotic events.

Recanalization

In patients receiving anticoagulation, the rate of venous recanalization in the follow-up is around 85% [67••]. Analysis of the available cohort studies indicates that this process predominantly occurs in the first few months after CVT, although it can take up to 1 year. An association between worse functional outcome and lack of venous recanalization has been recently shown in a meta-analysis of CVT patients treated with anticoagulation [67••]. More specifically, occurrence of recanalization was related to a 3.3-fold increase in the odds of complete functional recovery. However, the information on the temporal profile of recanalization was limited, hindering further conclusions on a possible critical time window for venous recanalization. Evidence on whether persistent occlusion increases the risk of CVT recurrence is even more scant, although an association has been shown in pediatric patients [68].

Follow-up imaging to establish the degree of recanalization can be useful to support or exclude the challenging diagnosis of recurrent CVT in patients who have worsening of complaints, as headache, during follow-up. Previous documentation of the extension of recanalization

facilitates the diagnostic work-up in patients with suspected recurrence.

CVT and Pregnancy

A pooled systematic review of 66 CVT cases during pregnancy/puerperium [69•] described an overall very good outcome, with complete recovery in 59% and independence in 94%. Not surprisingly, headache alone predicted excellent outcome while coma/obtundation predicted against excellent outcome. The comparison of management approaches with anticoagulation IA thrombolysis or thrombectomy failed to show any significant differences between those treatment modalities. Aguiar de Sousa et al. performed a follow-up study (median follow-up 14 years) of 119 women from the ISCVT cohort. Eighty-two new pregnancies occurred in 47 women. Eighty-three percent received some form of antithrombotic prophylaxis during at least one trimester of pregnancy or puerperium. The rate of recurrent venous thrombotic events was very low, with only 3 events, including one recurrent CVT [70••]. In a cohort of 52 pregnant women with previous CVT on antithrombotic prophylaxis with LMWH, no recurrent thrombosis or bleeding episodes were observed [71]. An updated systematic review on the safety of pregnancy after CVT reported a pooled incidence for CVT recurrence of 8 per 1000 and of 22 per 1000 for non-cerebral venous thrombosis. Stratification by antithrombotic prophylaxis showed a trend towards lower rates or recurrent events in women receiving heparin [72, 73•]. The European ESO/EAN Guidelines state that pregnancy is not contraindicated after CVT and suggest LMWH during pregnancy to prevent recurrent venous thrombotic events [39••].

Conclusions

Case control studies are needed to evaluate the strength of the association between several putative risk factors and CVT. Ideally such studies should be performed in countries and centers of diverse health care conditions, systems, and availability of resources. Given the low prevalence of CVT and the ubiquity of some of its presenting symptoms (e.g., headache), diagnostic studies of the cost-effectiveness of different imaging modalities and their combination to identify CVT are desirable. The appropriateness of screening acute CVT patients for some rare predisposing conditions must consider not only process indicators (i.e., reaching a diagnosis) but also patient-centered outcomes, i.e., whether performing screening prevents death, leads to a better functional outcome, or decreases psychological distress. In the near future, results of treatment trials on endovascular thrombolysis/thrombectomy (To-ACT), dabigatran (RE-SPECT CVT), and duration of anticoagulation (EXtending oral antiCOAgulation treatment after acute Cerebral Vein Thrombosis) will increase the level of evidence that currently supports the management of CVT.

Compliance with Ethical Standards

Conflict of Interest José M. Ferro reports personal fees from Boehringer Ingelheim (principal investigator RE-SPECT CVT trial) during the conduct of the study. Dr. Ferro also reports grants from Boehringer Ingelheim, outside the submitted work, and grants and personal fees from Bayer, outside the submitted work. Diana Aguiar de Sousa declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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