Cerebral venous and sinus thrombosis in adults: A Practical Approach

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Citation

Abstract
Thrombosis of the cerebral veins and sinuses (CVST) is relatively uncommon and often misdiagnosed. Certain populations such as children, pregnant woman or woman on OCT are at a higher risk. Its diagnosis has been made easier with the advance in CT venography and MRV. There is almost always an underlying hypercoagulable state that should be investigated. The use of anticoagulation is the treatment of choice. AED is used in selected cases. The prognosis is usually good unless the patient present with altered mental status or hemorrhage. In this paper we reviewed selected literature that has contributed to the actual practical knowledge on the diagnosis and treatment of CVST.

INTRODUCTION
Thrombosis of the cerebral veins and sinuses is relatively uncommon and often misdiagnosed. Its incidence is estimated to be around 0.22/100,000 annually in adults, 1 0.67 cases per 100,000 in children under 18 years 2 and 11.6/100,000 in obstetric patients 3. It can pose diagnostic and therapeutic challenges and without a high level of suspicion, can be easily missed or mistaken for other, more frequent neurological conditions.

However, during the last decade, cerebral vein and sinus thrombosis (CVST) is increasingly reported because of high medical awareness and advance in imaging techniques. Consequently, a number of case reports, retrospective and prospective studies are now available increasing our knowledge on this condition. Finally, the mortality from CVST classically ranging from 30 to 50% is nowadays less than 10%. 45 6 7

In this paper we reviewed selected literature that has contributed to the actual practical knowledge on the diagnosis and treatment of CVST.

ANATOMY OVERVIEW
The cerebral venous system is formed by deep and superficial veins that drain into the dural sinuses before returning the blood to the systemic circulation. The superficial veins include the superior anastomotic vein of Trolard lying across the parietal lobe and the inferior anastomotic vein of Labbe lying on the surface of the temporal lobe. Both veins drain the cortex and underlying white matter into the superior and inferior sagittal sinuses.

The deep cerebral veins (the basal or Rosenthal vein and deep internal cerebral veins) drain the deeper white matter, the basal ganglia and the diencephalon. Many deep cerebral veins drain into the great cerebral vein of Galen. The latter together with the inferior sagittal sinus returns the blood to the straight sinus. The straight and superior sagittal sinuses together form the two transverse sinuses that drain into the sigmoid sinuses returning the blood to the interior jugular veins. 8 9

PATHOPHYSIOLOGY
Venous drainage occlusion in the brain and subsequent venous congestion will have different manifestations depending on the venous system involved, the extent of the venous collaterals, the extent of the thrombosis and its duration. 10 The occlusion of a major venous sinus can impair the cerebral spinal fluid (CSF) resorption in the arachnoidal villi resulting in high intracranial pressure. Because the obstruction is in the arachnoidal villi, no gradient pressure will form, hence the absence of hydrocephalus on imaging. 11 Second, venous congestion can lead to parenchymal edema: Following venous thrombosis, the high venous pressure results in an increase in the net capillary filtration with the development of a vasogenic edema in the interstitial tissue drained by the thrombosed veins. Neurological signs secondary to that type of edema
Almost any brain syndrome can be secondary to a CVST and the level of suspicion of this condition should be high, especially in certain cases. For example in a pregnant woman or a young woman recently started on oral contraceptives, a young patient with subacute non resolving headache that develops seizures or a focal neurological deficit, an ICH in an unusual localization, a thunderclap headache, altered mental status, possibly transient global amnesia, visual disturbances, alexia.

Venous infarct can then result in small hemorrhages that may become confluent forming an intracerebral hematoma (ICH). The hematoma location is different from that of an arterial ICH and should raise the concern of CVST.

**ETIOLOGY AND RISK FACTORS**

CVST shares some common ground with the much more frequent lower extremity deep vein thrombosis (DVT). The three mechanisms of thrombosis defined by Virchow in the 19th century — vessel-wall injury, stasis, and “changes in the composition of blood” (hypercoagulability) — can be applied to CVST with minor stress on stasis (except when a brain tumor obstructs the venous drainage) and vessel wall injury. The major risk factor for CVST is inherited and/or acquired hypercoagulability disorders. 

Most of the time, a new event in a patient with underlying latent thrombophilia, will result in CVST. The use of oral contraceptives and pregnancy or puerperium are the one of the most frequent reported risk factors associated with CVST. Presence of Lupus anticoagulant, Factor V Leiden mutation, G20 210A prothrombin mutation, low folate level, hyperhomocysteinemia, deficiencies of anti–thrombin III, protein C, and protein S deficiency are commonly associated with CVST. Other less frequent systemic risk factors with CVST include but are not limited to vasculitis, intestinal inflammatory disease, leukemia, lymphoma and solid tumors outside the brain, choriocarcinoma, paroxysmal nocturnal hemoglobinuria, polycythemia vera, trombocythemia, steroids, oncology medications and dehydration. Finally, local causes like CNS infections, brain tumors, head and neck infections (used to be a leading cause), head trauma, spontaneous hypotension, jugular catheterization, surgery, lumbar puncture can be associated with CVST.

**PRESENTATION**

Almost any brain syndrome can be secondary to a CVST and
imaging of the cerebral venous system than time of flight (TOF) magnetic resonance venography (MRV) and is at least as accurate in detecting cerebral venous thrombosis. However, this techniques uses IV iodine for contrast which limit the use of CT venography in the case of pregnant women, children, patients in renal failure or who are allergic to iodine.

MRI: T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T2*/SWI (susceptibility-weighted) sequence are helpful when CVT is suspected. The absence of a flow void and the presence of altered signal intensity a cerebral sinus are indicative of a possible CVST. T2*-weighted (T2*SW) images can identify thromosed veins and sinuses more easily than any other nonangiographic MR sequence. T2*SW images can detect areas of hypointensities in the affected veins and/or sinuses, indicating the presence of intravenous clots. The signal in T1 is isointense in the acute phase then hyperintense in the subacute phase. In T2 it is initially hypointense and then hyperintense in the subacute phase. T2*SW images are more sensitive (90%) in the early phase than T1SE (84%). In addition, T2*SW is very sensitive (97%) in detecting isolated cortical CVST. Finally, the associated hemorrhagic venous infarcts were easily visualized on T2*SW images, but not T1- or T2-weighted images. Changes in the brain parenchyma (edema or hemorrhage) can be seen in around one third of cases.

MRV: Unenhanced time of flight (TOF) venography is the most common method used for diagnosing CVST. The images need to be assessed by an experienced radiologist because of the venous signal could be nulled depending on the venous flow and the plane of the image acquisition. Contrast-enhanced MRV is more sensible in the visualization of the small vessels as well as the dural sinuses and should be used when there is no contraindication to IV Gadolinium.

Transcranial color-coded duplex sonography (TCCS): TCCS has not been extensively studied in the assessment of CVST. It cannot however evaluate the anterior and mid portions of the superior sagittal sinus and cortical veins which limits its use in the diagnosis of CVST.

Conventional angiography: With the progress made with MRI and MRV in the last decade, conventional angiography is rarely needed.

D-dimer: the value of a negative D-dimer in ruling out CVST is controversial. D-dimer has an excellent negative predictive value in CVST. However, a negative D-dimer value should not prevent the clinicians from pursuing CVST investigations, especially in the setting of an isolated headache.

MANAGEMENT AND TREATMENT

Treatment of the underlying condition: the treatment of the underlying condition should be addressed. Withdrawal of the possible responsible drug, administration of steroids and/or immune suppressant in the case of vasculitis, antibiotics in case of infection...

Heparin: Unless contraindicated, patients with CVST should be started on UFH (target PTT between 70-90) or LMWH (weight adjusted). Dose adjusted UFH is not expensive and easily reversed in case of bleeding. It can be associated with HIT. LMWH poses less dosing issues, thus safer (less bleeding complications), and is easier to administer. In extracranial venous thrombosis it is more effective than UFH and has a better survival rate at follow up.

Heparin use in the CVST complicated by an ICH: In patients with ICH using heparin might increase the size of the hematoma leading to further complication. However several studies have shown that there is no evidence of increased risk of recurrent ICH in patients with CVST-associated hemorrhage treated with heparin. It is actually safe and beneficial to use heparin in those patients where actually not using the heparin might lead to further bleeding and worsening of the neurological state.

Coumadin: no prospective randomized trials have examined the optimal long term treatment of CVST. In particular, no data is available concerning coumadin treatment for CVST. The current guidelines are extrapolated from the management of extracranial venous thrombosis. In patients with a first episode of CVST it is recommended to give coumadin for 3 months if CVST was secondary to a transient risk factor, for 6–12 months in patients with idiopathic CVST and in those with mild hereditary thrombophilia. Indefinite coumadin therapy should be considered in patients with a recurrent episode of CVST and in those with severe hereditary thrombophilia.

Endovascular thrombolytic therapy: systemic or local injection of Urokinase or Alteplase can lead to a complete restoration of the venous flow with improvement of clinical outcome. It is associated with an increase risk of hematoma formation. The reported studies have a limited
number of patients and randomized controlled trials are necessary before any recommendations can be made as to whether thrombolytic therapy can be used as a primary modality of treatment in cases of CVST. It could be beneficial in the case of non response to anticoagulation therapy. Steroids use: Some author support the use of steroid to decrease vasogenic edema and reduce intracranial hypertension, however it was demonstrated that there is no benefit with patient treated with steroids over control subjects. Moreover steroid use in addition its effect on the GI, endocrine and immune system is known to have facilitate thrombosis and is actually a risk factor for CVST. Anti epileptic drugs (AED): up to 40% of patient with CVST have a seizures. AED should be used in the case of patients who presented with seizures because of high risk of recurrent seizures within 2 weeks. In addition prophylactic AED is highly recommended in supratentorial lesions and in patients with early seizures. Otherwise, prophylactic AED is not indicated.

Lumbar puncture: intracranial hypertension can be reduced and symptoms relieved through a therapeutic lumbar puncture. This is indicated in patients with severe headache and papilledema. Optic nerve fenestration should be considered in the case of possible loss of vision. If the increased cerebral pressure persists, the patient should have a lumboperitoneal shunt or ventriculoperitoneal shunt. Acetazolamide as temporary mean of decreasing the increased cerebral pressure could also be used.

Antiedema treatment: there is no evidence that antiedema treatment is effective. However the head should be elevated at least 30° regardless of the intracranial pressure. Hyperventilation with a target PaCO2 pressure of 30–35 mmHg can be attempted. Osmotic diuretics might be harmful because they decrease venous drainage.

Hemicraniectomy may be lifesaving in patients with parenchymal lesions leading to herniation.

**FOLLOW UP AND PROGNOSIS**

Recently, the overall mortality from CVT has become less than 10% 1,4,5,6,7,23,48. The major causes of death are transtentorial herniation (secondary to multiple lesions, diffuse edema, and/or a focal mass effect), cerebral anoxia due to seizure, and sudden cardiopulmonary arrest. 1,4,5,23

Factors associated with a higher mortality include altered mental status, coma, seizures, thrombosis of the superior sagittal sinus, cortical veins, and deep cerebral veins, parenchymal lesions, hemorrhagic lesions (particularly if the hematoma is >5 cm in its larger diameter), right hemorrhagic lesions, and posterior fossa lesion, male sex, age >37 years, central nervous system (CNS) infection, and cancer. Of all those factors coma and hemorrhage carry the highest risk of mortality. 1,4,5,6

Functional outcome: The functional outcome after a CVST is good. A recent review on the natural history of CVT included 1488 patients. 87.2% had a good outcome with complete or partial recovery, 8.7% had a poor outcome with permanent neurological deficits. At 12 or more months 88.3% had a complete or partial recovery, and only 9.7% had a poor outcome. 48,49

Revascularization: A study of 33 patients suggested that recanalization only occurs within the first four months following CVST and not thereafter, irrespective of oral anticoagulation. 50

Data from another study were similar showing that dural sinus thrombosis patients display a high spontaneous and intrinsic thrombolytic potential, with recanalization rates of 60% during the first 20 days. Afterwards the recanalization rates increase insignificantly. Recanalization had no influence on clinical outcome. 51

Recurrence: In the ISCVT the rate of recurrent sinus thrombosis was 2.2% over 16 months of follow-up. 41.5% of the recurrences occurred during anticoagulant treatment. The risk of DVT is even higher ranging from 4.3% to up to 15% of patients. 52

Conclusion: CVST should be suspected in any brain syndrome. Certain populations such as children, pregnant woman or woman on OCT are at a higher risk. Its diagnosis has been made easier with the advance in CT venography and MRV. There is almost always an underlying hypercoagulable state that should be investigated. The use of anticoagulation is the treatment of choice. AED is used in selected cases. The prognosis is usually good unless the patient present with altered mental status or hemorrhage. Thrombolyis appears to be very promising, however more studies are needed before its role is clearly defined.

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