Cerebral venous and sinus thrombosis in adults: A Practical Approach
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INTRODUCTION
Thrombosis of the cerebral veins and sinuses (CVST) 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%. 1-7

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

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. 8 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. 9 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.

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

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.
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.

The most common presenting symptom is headache (80-90 %) that could be isolated in up to 5% of cases. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), seizures (focal or generalized) and paresis were seen in up to 40% of patients, papilledema was present in around 30% while visual loss was seen in 13%. Mental status change and aphasia were reported in around 20% of patients, and approximately 10% presented with coma. Finally 5% had sensory signs.

In particular, thrombosis of the deep venous system is often dominated by severe dysfunction of the diencephalon, with coma, disturbances of eye movements and pupillary reflexes. Patients with deep venous system thrombosis tend to have a poor outcome.

**DIAGNOSIS**

Unenhanced computed tomography (CT) head is a rapid and useful imaging technique to rule out other causes of brain syndrome. It may show the first indications of venous sinus occlusion. It was already mentioned that parenchymal infarction or hemorrhage inconsistent with an arterial vascular territory should raise the suspicion of venous thrombosis. On head CT, during the first two weeks, the thrombus may be seen as linear high density in the vein or sinus. After two weeks, the thrombus becomes isodense to brain parenchyma and is usually seen only on contrast enhanced scans. Hyperattenuation of an occluded sinus can be seen in 25 % of cerebral venous sinus thrombosis. This sign is not specific and can be seen in patients with polycythemia, dehydration or subarachnoid hemorrhage. Contrast enhanced scanning can show the thrombus as a filling defect within the vessel, whereas the dura surrounding the clot are enhanced. This "empty delta" sign is found in 28.6% of cases, and is more readily detected if the clot is located in the superior sagittal sinus or torcula.

CT venography is a fast, widely available and accurate technique for detecting CVST. When care is taken while performing the maximum intensity projection (MIP) images three dimensional (3D) reconstruction, it gives more detailed...
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 thrombosed 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*-weighted images, but not T1- or T2-weighted images.

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 extracerebral 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 lumbo-peritoneal shunt or ventriculo-peritoneal 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 intracerebral 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%. 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. 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.

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.

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.

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.

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.

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. Thrombolysis appears to be very promising, however more studies are needed before its role is clearly defined.

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