Cerebral venous sinus thrombosis

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ABSTRACT

إن التخثر الجيبي الوريدي الدماغي هو مرض غير شائع ولكنه مرض عصبي خطير ذو عواقب وخيمة إذا لم يتم تشخيصه وعلاجه بشكل سريع وفوري. يعتبر هذا المرض مرض دماغي وعائي متميز ويصيب الأطفال والبالغين. أن النسبة التقديرية لحدوث هذا المرض هي حوالي 3 إلى 4 حالات لكل مليون نسمة سنوياً وتزيد هذه النسبة إلى 7 حالات لكل مليون نسمة سنوياً لدى الأطفال. قد يخفق الأطباء بتشخيص المرض خصوصاً في حضوره الأولي السريري أو الاشعاعي ولذلك يجب أن يكون مؤشر الشك لدى هؤلاء الأطباء عالي. خلال العقود الماضية زادت نسبة الوعي لمثل هذا التشخيص كما تحسنت طرق وأساليب التشخيص الإشعاعي وأصبح هناك كثير من الأدوية الفعالة وبذلك تحسنت عواقب هذا المرض وأصبح الشفاء التام ممكن. في هذا المراجعة نحن نقوم بتحليل جميع المعلومات التي تخص هذا المرض ونرفع من معدل الوعي لدى أطباء الأعصاب والباطنة المتخصصين في علاج المصابين بهذا المرض.

Cerebral venous thrombosis is a rare serious neurological disorder that may cause vital or morbid consequences if not diagnosed and treated promptly. It is a unique cerebrovascular disorder that predominantly affects adults in their third and fourth decades. The incidence of CVST in adults is estimated to be 4 cases per million of the population, and 7 cases per million in children. In the last 2 decades, the awareness and prognosis of the disease have improved due to development of sophisticated neuroimaging techniques and effective treatment. This comprehensive review of the topic aims to improve knowledge among neurologists and internists who are involved in the management of these patients.

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Cerebral venous sinus thrombosis (CVST) is a rare and distinct cerebrovascular disorder with highly variable clinical presentation. It has been recognized since 1825 when Ribes[1] described the clinical history and postmortem examination of a 45-year-old man who died after a 6-month history of headache, seizures, and delirium. An autopsy revealed widespread malignancy and thrombosis of multiple sinuses. In comparison with other causes of stroke, CVST has a high potential for recovery if adequate therapeutic measures are applied early in the course of the disease. We review the topic of CVST with emphasis on epidemiology, clinical presentations, causes, and treatment. This review will help physicians of different subspecialties including neurology (adults and pediatrics), emergency physician and internists, to diagnose the affected patients as early as possible and to treat them promptly.

Epidemiology. The syndrome of CVST may affect patients of all ages including neonates; however, it has a specific predilection for young adults and children. Due to lack of well-designed epidemiological studies, the true incidence of CVST is unknown. In a study performed in England and Wales between 1952 and 1961, Kalbag and Wolf[2] concluded that CVST was the principal cause of death in only one per 2 million persons per year. However, a study performed by Towbin[3] found CVST in 9% of 182 consecutive autopsies. The currently accepted annual incidence is 3 to 4 cases per one million populations in adults, and up to 7 cases per one million among children.[4] The incidence of CVST is possibly higher than previously thought. This is mainly due to increased awareness of the disease, and availability of more sophisticated neuroimaging techniques. In adults, the incidence is higher in females (75% of cases). This could be explained by the occurrence of pregnancy and puerperium (both considered as hypercoagulable states), and the intake of the hormonal contraceptive therapy. Female preponderance is lacking in children.

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In one study, the mean age of patients affected by CVST was 29.5 years.[5] The estimated incidence of CVST in pregnant women is 12 cases per 100,000 deliveries.[6] Pregnancy and puerperium are well-known predisposing conditions for CVST. Both conditions are prothrombotic states due to the occurrence of several physiological changes in the coagulation system including reduction in protein S levels, increases in activated protein C resistances, plasminogen activator inhibitor, fibrinogen, prothrombin fragments one and 2, and coagulant activity of factors V and VIII. In addition, platelet undergoes increase aggregability, and reduces responsiveness to prostacyclin and cAMP formation.[7] In Saudi Arabia, the incidence of CVST is unknown, and 3 studies are reported with a total of 173 cases.[5] A nationwide epidemiological multicenter study or registry is recommended as current statistics are lacking.

Pathophysiology. The exact pathophysiology mechanism, which contributes to the appearance of clinical features of CVST is thought to be a combination of increased venular and capillary pressure and decreased CSF absorption. The rise in venous pressure will cause reduction in cerebral perfusion with subsequent ischemic injury, cytotoxic edema, disruption of the blood-brain barrier (leading to vasogenic edema), and rupture of the vessel wall culminating in parenchymal hemorrhage.[8] On the other hand, CVST may impair CSF absorption with subsequent elevation of intracranial pressure. This in turn will worsen venular and capillary hypertension and contribute to vasogenic and cytotoxic edema and parenchymal hemorrhage.[8]

Clinical presentations. The clinical presentation of CVST is highly variable, nonspecific, and cannot be diagnosed on clinical grounds alone (**Table 1**). The presentation is usually subacute (50-60%), but it could be acute (20-30%), or chronic (10-20%). Headache is the most predominant symptom in many studies (70-95%).[4,9] It can be localized or generalized and may worsen with Valsalva maneuvers.[8] Other associated features include seizures, papilledema, cranial nerve palsy, focal neurological deficit, and altered level of consciousness. In 2 studies, focal neurological deficits (including hemiparesis, monoparesis, or paraparesis) were the presenting feature in 37%[6] and 43%.[8] Seizures, partial or generalized, are more frequent in CVST than in other stroke types. Seizures occurred in 39-47% of patients.[6,10] They are more typical in patients with sagittal sinus and cortical vein thrombosis, parenchymal lesions, and focal motor or sensory deficits.[11] The clinical presentation of CVST is strongly influenced by the site and extent of thrombosis. In cavernous sinus thrombosis, patients may present with orbital pain, chemosis, proptosis, and cranial nerves palsies (III, IV, and VI). When the deep cerebral venous system is occluded (straight sinus and its branches), the clinical picture is rapidly progressive, more severe, and bilateral with coma, confusion, mutism, dysarthria, and motor deficits (**Figure 1**). Other unusual presentations of CVST include thunderclap headache, episodes of migraine with aura, psychiatric symptoms, vestibular symptoms including tinnitus, cranial neuropathies, and subarachnoid hemorrhage.[6] A characteristic, but rare, presentation is the occurrence of unilateral hemispheric symptoms and signs followed within days by symptoms and signs due to involvement of the other hemisphere. These are usually caused by the development of parenchymal lesions on both sides of the superior sagittal sinus. If a large unilateral infarct or hemorrhage develops, patients may become comatose or die from uncal herniation and brain stem compression if untreated. Patients may also present with isolated

Table 1 - Presenting symptoms of cerebral venous sinus thrombosis.

Common symptoms	Rare symptoms
Isolated intracranial hypertension	Cavernous sinus syndrome
Focal syndrome (deficit and/or seizure)	Subarachnoid hemorrhage
Diffuse encephalopathy	Thunderclap headache
Any combination of the above	Attacks of migraine with aura
	Isolated headache
	Transient ischemic attacks
	Tinnitus
	Isolated psychiatric symptoms
	Isolated or multiple cranial nerve palsies

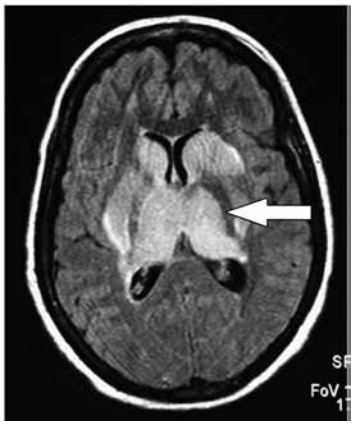

Figure 1 - Flair T2-weighted MRI image demonstrating bilateral increased signal intensity in the basal ganglia, thalami, and heads of caudate nuclei.

intracranial hypertension.[8] Patients in this category usually present with headache, diplopia (involvement of the sixth nerve) and papilledema.[12] Severe papilledema can cause blurring of vision, decrease acuity, and even permanent blindness if left untreated.

Etiology and site of thrombosis. The literature describes 75-85% of cases with known etiological factors.[4] Conditions that may predispose to CVST are divided into infective or non-infective, and not uncommonly more than one cause might be found in an individual patient. Fortunately, due to early diagnosis and the availability of antibiotics, the frequency of infectious causes has declined and represents only 6-12% of adults with CVST.[6,13] Infectious causes include CNS infections, infections of the ears, mastoids, sinuses, mouth, face, or neck, and systemic infections (for example, neonatal sepsis). Cavernous sinus thrombosis is a well-known complication of infection of the face, especially the dangerous triangle. The most common organism in this situation is *Staphylococcus aureus*. Non-infective causes include pregnancy, puerperium, genetic hypercoagulable states and all predisposing conditions for deep vein thrombosis in the legs, malignancy, and systemic conditions such as connective tissue diseases, and vasculitis.[6,8] Genetic prothrombotic disorders include factor V Leiden mutation, protein C and protein S deficiency, antithrombin deficiency, prothrombin mutation (the substitution of A for G at position 20210), and homocystinemia caused by gene mutations in methylenetetrahydrofolate reductase.[8] Lumbar puncture, jugular venous cannulation, trauma, and neurosurgical procedures can cause or lead to CVST.[6,8] The possible underlying mechanism is low CSF pressure, which causes a downward shift of the brain with traction and deformation of the cortical veins and sinuses. The diagnosis of CVST after a lumbar puncture might be difficult, and a high index of suspicion is needed. The treating neurologist may attribute headache to the lumbar puncture (post-lumbar puncture headache) and not to sinus thrombosis. The largest published cohort study reported by Ferro et al[6] showed that the most common sinuses affected are the superior sagittal sinuses and transverse sinuses (**Figure 2**). The deep venous system is involved in 10.9%, and the cavernous sinuses are involved in 1.3%, and in the vast majority of cases, thrombosis affects several sinuses, and/or veins.[6]

Diagnosis. Cerebral venous sinus thrombosis is an acute neurological condition that needs appropriate treatment with anticoagulation, and early diagnosis is mandatory. Since the clinical presentation is highly variable, a high index of suspicion is necessary. The diagnosis should be considered in young patients with recent unusual headache or stroke-like symptoms in the absence of the usual vascular risk factors, in patients with signs of intracranial hypertension, and in patients with neuroimaging evidence of hemorrhagic infarcts, especially if the infarcts are multiple and not confined to the arterial vascular territories. A CT without contrast (unenhanced) is the preferred and the most frequently performed initial radiological examination in the emergency department. This will help to rule out other cerebral disorders such as subarachnoid hemorrhages, and to show venous infarcts/hemorrhages. However, it has poor sensitivity and shows direct signs of CVST in only one third of patients.[8,14] The classical signs are the cord sign (thrombus in a sinus or even a cortical vein), and the dense triangle, or empty delta sign (thrombus in the superior sagittal sinus). **Figure 3** illustrates direct and indirect signs on CT. The MRI with magnetic resonance venography (MRV) are the current gold standard neuroimaging modalities for the diagnosis of CVST.[13] The MRI will visualize the thrombosed vessel, and MRV will detect the non-visualization of the same vessel (**Figure 4**). Limitations of MRI include flow artifacts (that can lead to false positives) and the absence of hyperintense signal on T1 and T2-weighted images at the onset of acute thrombosis. Limitations of MRV include difficulty to differentiate between thrombosis and hypoplasia of lateral sinuses. In addition, MRI/MRV is time consuming and has limited utility in

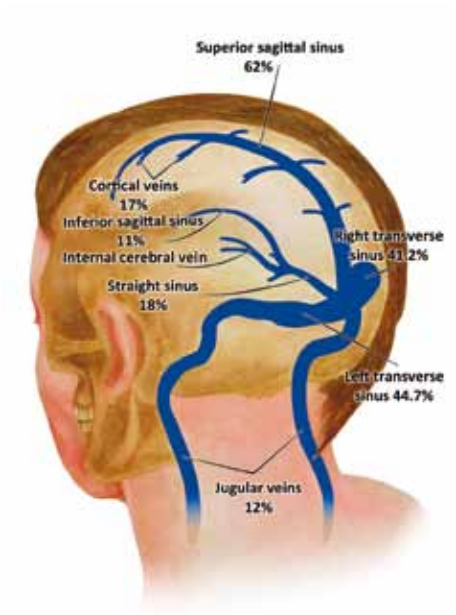

Figure 2 - Frequency of thrombosis of the major cerebral veins and sinuses.

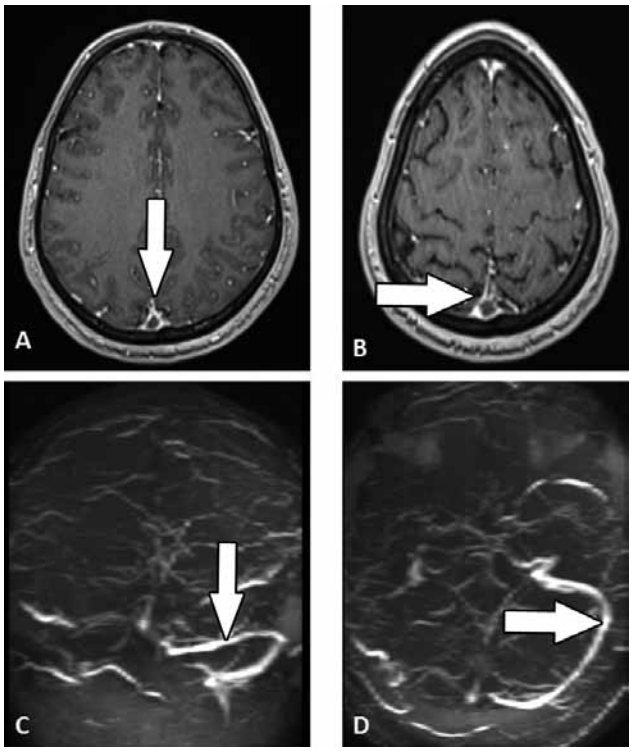

Figure 3 - Dense triangle sign on T1-wighted MRI with gadolinium (**A** & **B**). Magnetic resonance venography showing non-visualization of superior sagittal sinus and right lateral sinus (**C** & **D**).

claustrophobic patients and those with renal impairment (the associated risk of nephrogenic systemic fibrosis).[8] Computed tomographic venography (CTV) is a rapid and reliable method for detection of CVST. It allows the detection of thrombus of heterogeneous density and is considered comparable to MRV. Concerns with this technique include radiation exposure, contrast allergy, and nephrotoxicity.[15] If the diagnosis is still uncertain after CT/CTV or MRI/MRV have been performed, cerebral angiography may provide better details of the cerebral sinuses and veins. Specific indications or cases include isolated thrombosis of the cortical veins and cases with dilated and tortuous "corkscrew" veins, which are evidence of thrombosis downstream in the sinuses. Several studies have tested the value of D-dimer measurements in the diagnosis of CVST.[16,17] Although elevated D-dimer support the diagnosis of CVST, it has a false positive rate of 9%, and a false negative rate of 24%.[8,16] Screening for hypercoagulable conditions should be performed in patients presenting with CVST. This includes evaluation for factor V Leiden mutation, prothrombin gene mutation 20210, lupus anticoagulant, anticardiolipin antibodies, hyperhomocysteinemia, protein C and protein S deficiency, and antithrombin. Blood for hypercoagulable state screening should be withdrawn before the initiation of anticoagulation therapy.[8,9]

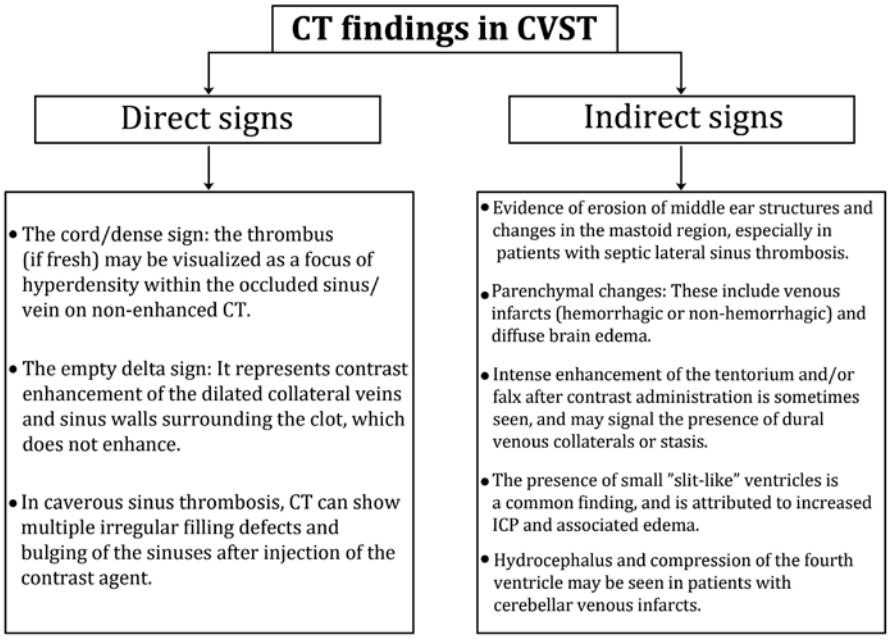

Figure 4 - Computerized tomography (CT) findings in cerebral venous sinus thrombosis (CVST).

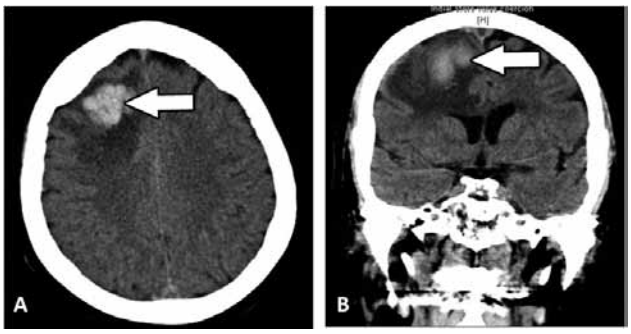

Figure 5 - Computerized tomography **A)** axial, and **B)** coronal showing intracerebral hemorrhage due to cerebral venous sinus thrombosis.

Complications. Intracerebral hemorrhage (ICH) occurs in 15-49% of patients[18] (**Figure 5**). An ICH in CVST is commonly intracerebral. but subarachnoid hemorrhage (SAH) and subdural hemorrhage (SDH) have been described.[19] In these circumstances, the diagnosis should be secured. Anticoagulation of conditions mimicking CVST such as aneurysmal SAH may cause fatal consequences. Pulmonary embolism and deep vein thrombosis are fatal complications of CVST. The majority of these cases occur within the first year. Pulmonary embolism occurs in 11.3% of cases with a mortality rate of 95.6% of cases. Other complications include hypopituitarism (resulting from cavernous sinus thrombosis, status epilepticus, intracranial hypertension, uncal herniation, hydrocephalus, and death).[8]

Treatment. On the basis of several studies (meta-analysis, randomized trials, and a large open series such as the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT),[14] anticoagulation is considered the first line therapy of CVST. This is a safe and effective modality of treatment of CVST with or without intracranial hemorrhage at presentation. Either dose-adjusted, intravenous unfractionated heparin, or body-weight-adjusted subcutaneous low-molecular weight heparin can be used.[20] They are used as a bridge to oral anticoagulation with a vitamin K antagonist. Systematic reviews of thrombolysis in CVST show lack of evidence to support their routine use (local or systemic) in this disorder.[9,11,13] The majority of patients recover with anticoagulation therapy, and only a small percentage of patients have poor outcome despite anticoagulation. If patients are not improving despite an appropriate dose of anticoagulation, thrombolysis with or without thrombectomy may be considered. This should be carried out in selective centers by an expert interventional radiologist. In patients with severe intracranial hypertension, treatment should include raising the head of the bed, admission to an ICU with sedation, treatment with mannitol, hyperventilation, and monitoring the intracranial pressure. If papilledema threatens vision, a lumbar puncture should be considered, which is usually successful in improving visual function and headache. Using steroids does not show benefit, even in patients who have parenchymal lesions. Surgical thrombectomy is rarely necessary, and is usually reserved for the rare circumstances in which clinical deterioration occurs despite maximal medical therapy. Craniectomy or hematoma evacuation is reserved for those patients who have large parenchymal lesions causing herniation. These decompressive surgical procedures have been associated with improved clinical outcome.[21]

Prognosis. Between 57-86% of patients have complete functional recovery,[5] and the mortality ranges between 5.5-18% in different series.[22] There is no clear correlation between disease severity, and factors indicating poor prognosis include extremes of age (infancy and advanced age), rapid onset with coma and focal deficits, thrombosis affecting largely the deep venous system, and the nature of the underlying condition (particularly sepsis, malignancy, and paroxysmal nocturnal hemoglobinuria). Other reported poor prognostic factors are CNS infection, intracranial hemorrhage, low Glasgow coma scale on admission, mental status disorder, or male gender. Causes of death include transtentorial herniation, multiple lesions, status epilepticus, medical complications, and pulmonary embolism. Between 2.8-12% of patients suffer from CVST recurrence.[22] The predictors of recurrent thrombosis include persistent venous occlusion on follow up imaging, heterozygosity for the G20210A mutation in factor II, and the lack of anticoagulation therapy. The outcome of CVST is therefore, generally favorable and potentially aggressive therapeutic intervention should be confined to those patients who deteriorate rapidly despite anticoagulation, or those who demonstrate poor prognostic indicators.[23]

In conclusion, CVST is an uncommon but serious acute neurological disorder with a highly variable clinical presentation. Unlike arterial stroke, it often affects young adults and children with a female preponderance. Over the past decade, CVST has been diagnosed more frequently due to increased awareness and availability of better non-invasive imaging techniques. Cerebral venous sinus thrombosis is a condition that needs early diagnosis and appropriate treatment with anticoagulation. Anticoagulants with dose-adjusted intravenous heparin or body-weight-

adjusted subcutaneous low-molecular-weight heparin are the mainstay of treatment. However, in a few cases, more aggressive treatments such as mechanical thrombectomy, local intravenous thrombolysis, and decompressive craniectomy may be required.

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