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REVIEW

Cerebral venous thrombosis—A primer for the haematologist

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ABSTRACT

Cerebral venous thrombosis (CVT) is a condition that can affect all age groups and can often be difficult to diagnose and treat. The difficulties in diagnosis are mainly due to the non-specific presenting features of CVT, which can range from isolated headache and visual or auditory problems, to serious symptoms such as hemiparesis and coma. Therefore, it can present to various specialists including general physicians, obstetricians and neurologists. In recent years, more widespread use of cerebral imaging has led to the diagnosis being made more often. Since thrombosis is the key component, haematologists are consulted in the management of these patients including for identification of a causative factor for CVT. In this regard, the pivotal International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) has shed more light on its epidemiology and management options. This review aims to provide guidance to haematologists when faced with a patient with CVT, based on the currently available evidence.

1. Introduction

Cerebral venous thrombosis (CVT) is a rare condition which accounts for 0.5–1% of all strokes [1]. The Cerebral Venous Thrombosis Portuguese Collaborative Study Group identified 91 new cases from 20 neurology specialist centres in the country, whilst a more recent cross-sectional study reported 94 patients from 19 hospitals giving an overall incidence of 1.32 per 100,000 person-years [2,3].

Women are three times more likely to experience a CVT compared to men, with the risk being particularly raised in pregnancy and with the use of oral contraceptives. The Dutch cross-sectional study noted that amongst women between the ages of 31 and 50 years, the incidence was 2.78 per 100,000 person-years [4]. In children, it is extremely rare as noted in the Canadian Paediatric Ischemic Stroke Registry (0.67 cases per 100,000 children per year), although in those studied, neonates were most commonly affected [5] with the most common predisposing factor being infection or dehydration [1]. Majority of cases occur in the younger age group, with nearly 80% of 624 cases in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) occurring in patients less than 50 years of age [4].

Due to the varying presentations and probably the lack of awareness, there is often a delay in the diagnosis of CVT. In the ISCVT, the median delay from onset of symptoms to hospital admission was 4 days (mean 14.5 days, SD = 54.7 days), and from symptom onset to diagnosis, 7 days (mean 18.3 days, SD = 59.4 days) [6,7]. A delay in diagnosis is associated with both higher morbidity and mortality, such as visual defects and dependency [7]. This review aims to provide a structured overview of CVT in order to raise awareness of the diagnosis and management of the disease for the non-specialist.

2. How do patients with CVT present?

CVT can present with many diverse features which predominantly depend on i) the location of the thrombosis, ii) the time between onset of symptoms and hospital admission, and iii) the presence of parenchymal brain involvement [1]. Clinical syndromes at presentation can be divided into four groups; i) isolated intra-cranial hypertension, ii) focal neurological signs, iii) encephalopathy and iv) cavernous sinus syndrome [1]. There may also be overlap between these four patterns. Scenarios that point to a possible diagnosis can be seen in Table 1.

Headache is the most common symptom of cerebral venous thrombosis, present in up to 89% of patients [6,8]. It is commonly the first symptom (80%), and can sometimes be the only symptom [8]. The headaches are usually localised rather than diffuse [9], but a diffuse pattern can be seen with raised intracranial pressure. It has no specific pattern but is usually persistent. Although most often gradual in onset, cases with sudden onset mimicking that of a subarachnoid haemorrhage have been reported [10,11]. Whilst the underlying reason for the development of headache in CVT is not entirely known, it is thought that the occlusion of a cerebral vein leads to decreased cerebrospinal fluid (CSF) absorption, hence resulting in increased intracranial pressure, which can stretch the nerve fibres in the vessel walls. An alternate explanation is local inflammatory reaction from the thrombus, bearing in mind that clot products are potent pro-inflammatory substances

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Table 1
When should CVT be suspected?

Scenarios which would instigate investigation of suspected CVT [54]
Headache • in a pregnant female in the third trimester • in a young female who recently started oral contraceptives • of an atypical nature, persistently, in young individuals
Stroke in the absence of well-known cardiovascular risk factors
Radiological evidence of haemorrhagic infarcts not in a particular vascular distribution
Intracranial hypertension in the absence of an explanation
Multiple haemorrhagic infarcts
Ophthalmological symptoms in an individual with recent sinusitis

(similar to post-thrombotic syndrome following lower limb deep vein thrombosis). Headaches resulting from increased intracranial pressure are characteristically worse on lying down and can be associated with transient visual disturbances, often on coughing or sneezing. In ISCVT, a higher frequency of headache was found in women who developed CVT on oral contraceptives or during pregnancy [4]. However, it can be difficult to distinguish this from i) migraines, which can also be associated with oral contraceptives and ii) low CSF volume headache, which can develop after epidural anaesthesia.

Focal neurological symptoms and signs can also occur in patients with CVT [6]. Most commonly, in 37% of cases, this includes motor weakness; monoparesis, hemiparesis or bilateral involvement. Sensory and visual deficits are less common. Seizures are also a common feature of presentation, with up to 39% presenting with focal or generalised seizures, which includes status epilepticus (much more common than in cases of arterial stroke, making a presentation with features of arterial stroke and seizures suggestive of CVT) [6]. Encephalopathy has been reported in severe cases of CVT. Additionally, CVT can have an insidious presentation with papilloedema and normal CT (mimicking idiopathic intracranial hypertension), or on the other extreme of the spectrum, can also present with raised intracranial pressure and coma [6].

In general, signs and symptoms of CVT are governed by the location of the thrombus in the cerebral vein distribution, details of which can be found in Table 2 (anatomy of the cerebal veins are given in Fig. 1). The most commonly thrombosed sinuses in previous reports are the transverse, sigmoid [12] and superior sagittal [13] sinuses; accounting for 41.2–70% [3,6], 53% [3], and 62% [6] respectively. Parenchymal lesions were seen in 44% of the cases [3].

In the ISCVT, diagnosis was achieved within 48 h of onset of symptoms in 37.2% of patients, within 48 h to 30 days in 55.5% of patients, but more than 30 days in 7.2% of patients [6].

Table 2
Location of thrombi and corresponding symptoms adapted from Bousser and Ferro [1].

Location of thrombus	Signs/symptoms
Cavernous sinus thrombosis	Ocular signs - orbital pain - chemosis - proptosis - oculomotor palsy
Cortical vein thrombosis	Motor deficits Sensory deficits Seizures
Sagittal sinus thrombosis	Motor deficits Bilateral deficits Seizures
Lateral sinus thrombosis	Isolated intracranial hypertension
Left transverse sinus thrombosis	Aphasia
Deep venous sinus (straight) thrombosis	Behavioural symptoms (thalamic lesions)

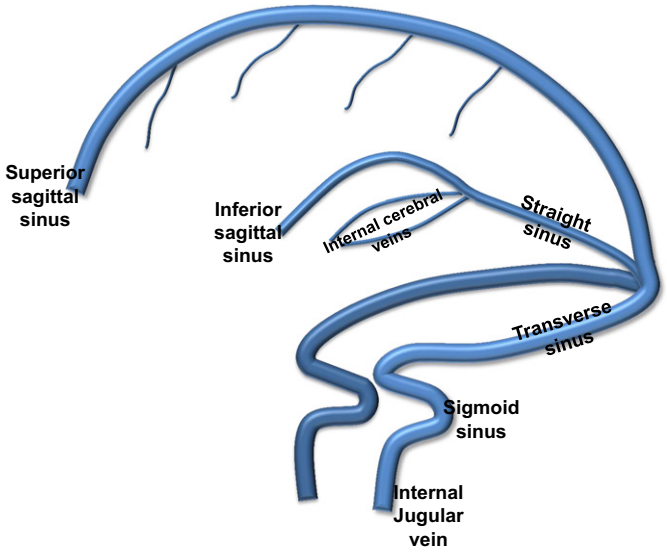

Fig. 1. A schematic of the major components of the cerebral venous system.

3. How is CVT diagnosed?

D-dimer is often used in conjunction with a clinical probability score for the diagnosis of venous thromboembolism. In the case of CVT, a positive D-dimer supports the diagnosis, but a normal D-dimer does not exclude the possibility of a CVT, as up 10% of patients with CVT had normal D-dimers [14]. In patients with a brain parenchymal signs or seizures, D-Dimer is positive in most cases (normal in only 4%), but in those presenting with isolated headache, up to a quarter have normal D-dimers [14].

In the ISCVT, diagnosis was established by Magnetic Resonance Imaging (MRI) or MR venography in 71%, by intra-arterial angiography in 12% and by Computerised Tomography (CT) venography in 2%, whilst multiple imaging modalities were needed in 14%. Diagnosis in the remaining 1% was established by autopsy or surgery [6].

MRI by gradient echo T2 susceptibility weighted sequences used in conjunction with MR venogram is the most sensitive imaging modalities to diagnose a CVT [15–20]. The disadvantage of isolated MR venography is that if the diagnosis is based on lack of blow flow only, this could be due to frequent anatomical variance (e.g. hypoplasia of lateral sinuses) [21–23]. On the contrary, MRI without a venography may not pick up a CVT since imaging of the venous system itself is necessary to identify the thrombus and the consequent lack of blood flow.

As accessibility to MR scans is not widespread, CT combined with CT venogram can also be used [24]. The AHA/ASA guidelines consider it equally sensitive with an overall sensitivity of 95%, but a number of disadvantages should be considered. These include high exposure to radiation and use of contrast material, thereby the possibility of allergic reactions and nephropathy [21]. An advantage of CT modality is that, although normal in 30% of CVT cases, it may be useful to rule out other sub-acute or acute conditions (such as facial sinus infections) contributing to the clinical picture [25].

Should a diagnosis of CVT still be suspected after inconclusive use of CT and MR modalities, cerebral intra-arterial angiography can be used [21]. This may be particularly helpful in diagnosis of cortical vein thrombosis. The AHA/ASA guidelines also recommend an early follow-up CT or MR venogram in patients with persistent or evolving symptoms to rule out propagation of thrombus.

A lumbar puncture (LP) can show non-specific changes in patients with CVT (such as lymphocytic pleocytosis, increased levels of RBCs and protein [26,27], but is not recommended for diagnostic purposes unless meningitis is suspected as a differential diagnosis [21]. It can be helpful to demonstrate raised intracranial pressure, where it may be