Cerebral Venous Sinus Thrombosis

JK Lovett & A Pinto

Key points:
- Clinical presentation of CVST may mimic subarachnoid haemorrhage, encephalitis, eclampsia, idiopathic intracranial hypertension and arterial stroke.
- Most symptoms are caused by either raised intracranial pressure or focal cerebral infarction or haemorrhage.
- The diagnosis of CVST may be missed on plain CT and magnetic resonance venography is the investigation of choice.
- Management includes hydration, seizure control, reduction of CSF pressure, and treatment of underlying causes.
- Carefully administered anticoagulation is recommended and may be beneficial even in the presence of intracranial haemorrhage.

Introduction

Cerebral (or dural) venous sinus thrombosis (CVST) is a condition distinct from other cerebrovascular disease, which presents its own particular diagnostic difficulties and treatment controversies. The clinical presentation is variable and may mimic a wide range of other neurological disorders that include subarachnoid haemorrhage, encephalitis, eclampsia, idiopathic intracranial hypertension and arterial stroke. Furthermore, CVST may not be obvious on conventional brain imaging, and the diagnosis may be missed without adequate clinical suspicion and proper venography. Consequently, little is known about the true epidemiology of CVST. The estimated annual incidence is between 3 and 8 per one million population, but this is likely to be an underestimate.[1–2] The mean age of diagnosis is 39 years, and women account for approximately 75% of cases, reflecting the association with pregnancy and oral contraceptive use.[3] The frequency of CVST in association with pregnancy is reported to be 12 per 100,000 deliveries,[4] but this figure is likely to be much higher in developing countries.

Aetiology

There are many reported causes of CVST (Table 1), but in a significant minority of at least 12%, no cause can be found even after extensive investigation and follow-up.[3] Pregnancy remains one of the most significant risk factors for CVST, and is associated with almost 20% of cases in young women.[3] CVST may occur in all stages of pregnancy, but the highest risk is in the second or third week postpartum. In a US study, factors associated with increased CVST puerperial risk were caesarean delivery, pregnancy associated hypertension, and coexistent infection.[4] In developing countries, the risk of puerperial CVST is especially high, probably due to higher rates of infection and dehydration. In India, the CVST is reported to occur in 4.5 per 1000 deliveries and to be responsible for 25% of maternal deaths.[5]

The oral contraceptive pill is the most studied and most commonly reported drug-related risk factor in CVST. Data from a prospective case-control study found a significantly higher proportion of women with CVST used oral contraceptives than those

Local
- Infections (sinusitis, mastoiditis, otitis, facial cellulitis, meningitis)
- Tumour
- Head injury
- Neurosurgical procedures
- Lumbar puncture
- Jugular vein catheterisation

Systemic
- Genetic thrombophilic conditions (Protein C and S deficiencies, Factor V Leiden mutation, Antithrombin III deficiency, Prothrombin mutation, homocysteinaemia, sickle cell trait)
- Dehydration
- Systemic infection
- Pregnancy and puerperium
- Malignancy
- Nephrotic syndrome
- Antiphospholipid syndrome
- Systemic inflammatory conditions (Behcet's syndrome, sarcoid, inflammatory bowel disease, SLE)
- Drugs (oral contraceptive pill, hormone replacement therapy, ecstacy, asparaginase)
- Haematological disorders (polycythaemia, thrombocythaemia, leukaemia, paroxysmal nocturnal haemoglobinuria)

Table 1. Causes and risk factors for cerebral venous sinus thrombosis.

Joanna K Lovett
MB ChB DPhil MRCP
Specialist Registrar
Neurology
Wessex Neurological Centre
Southampton General Hospital
Southampton

Ashwin Pinto
MA DPhil MRCP
Consutant Neurologist
Wessex Neurological Centre
Southampton General Hospital
Southampton

Correspondence:
Dr Joanna K Lovett
Wessex Neurological Centre
Southampton General Hospital
Tremona Road
Southampton SO16 6YD
Tel: 02380777222
Email: joanna.lovett@suht.swest.nhs.nuk

without (age adjusted odds ratio (OR) = 13). The association was highest in those who used the oral contraceptive and who also had a genetic prothrombotic defect, compared with women who had neither risk factor (OR = 30).[6]

Infections of the paranasal sinuses, ears, mastoids, face, orbits and meninges have become less common causes of CVST since the advent of antibiotics, but probably still account for up to 12% of all CVST.[3] The exception is cavernous sinus thrombosis, which is nearly always associated with an underlying infection of the ethmoid or sphenoid sinuses, orbit or face.

Mechanical trauma to the venous sinuses or jugular veins also increases the risk of thrombosis. Causes include head or neck injury, tumour, craniotomy and jugular venous cannulation. Lumbar puncture is also reported to precipitate CVST, especially in the presence of another thrombophilic risk factor, perhaps because of traction on the cerebral veins following CSF removal.[7]

Pathogenesis

The venous drainage of the brain is made up of three components: the superficial cortical veins, the deep cerebral veins, and the venous (dural) sinuses (Figure 1). These connect with each other and also with the veins that drain the meninges, scalp, face, orbits and nasal sinuses. When thrombosis occurs, it is usually found in at least one of the major venous sinuses, most commonly the superior sagittal (62%) or transverse (86%) sinuses.[3] If the sinuses occlude, this leads to venous hypertension, reduced absorption of cerebrospinal fluid (CSF), and, consequently, raised intracranial pressure. This is not normally associated with ventricular enlargement (hydrocephalus) because there is no obstruction to CSF flow prior to absorption and therefore no pressure gradient between the CSF in the ventricles and the brain surface. Thrombosis of the cortical and deep cerebral veins, which usually accompanies sinus thrombosis, causes local swelling of the brain parenchyma, which may lead to haemorrhage and venous infarction.

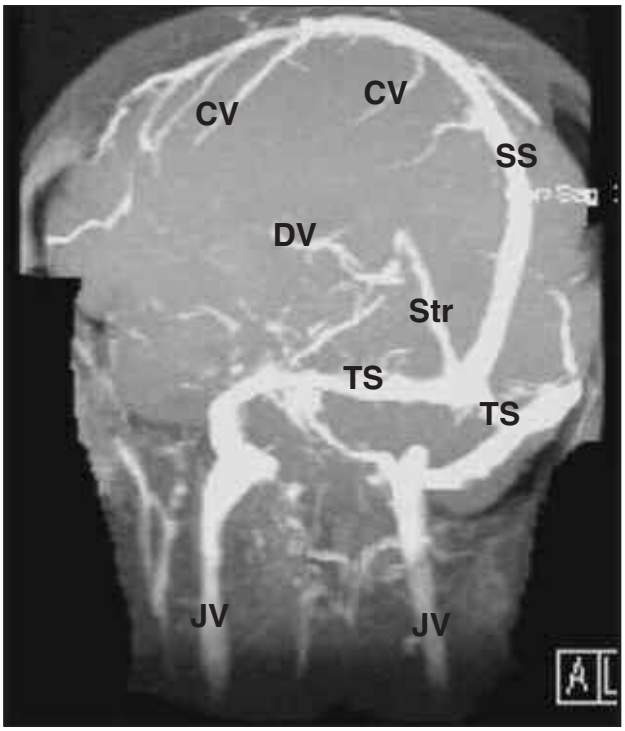

Figure 1. Normal magneteic resonance venogram. **SS**: Sagittal Sinus, **Str**: Straight Sinus, **TS**: Transverse Sinus, **JV**: Jugular Vein, **CV**: Cortical Veins, **DV**: Deep Cortical Veins.

Clinical features

The clinical features are highly variable in both nature and rapidity of onset (Table 2), but most can be divided into one of the two following categories:

Headache	89%
Seizures	39%
Paresis (usually hemiparesis, occasionally bilateral)	37%
Papilloedema	28%
Altered mental state	22%
Aphasia	19%
Stupor or coma	14%
Diplopia	14%
Visual loss	13%
Sensory symptoms	5%

Table 2. Frequencies of common clinical features of cerebral venous sinus thrombosis in 624 patients enrolled into an international study of prognosis.[3]

Symptoms that arise from raised intracranial pressure

Headache is the most common symptom of CVST and occurs in at least 89% patients.[3,8] Occasionally, the onset of headache is sudden, and indistinguishable from that arising from subarachnoid haemorrhage.[9] Papilloedema, visual failure or a sixth nerve palsy may also occur. In 20%, these are the only features and the clinical picture is indistinguishable from idiopathic ("benign") intracranial hypertension (IIH).

Symptoms that arise from focal areas of venous hypertension, infarction and haemorrhage

Altered consciousness or behaviour (50%), focal or secondary generalised seizures (39%) and hemiparesis (37%) are all common at presentation.[3,8] Unlike most arterial strokes, venous infarction does not respect the arterial territories and the clinical syndrome may evolve over time. For example, a hemiparesis with aphasia may progress to a quadriparesis as both hemispheres either side of a sagittal sinus thrombosis become ischaemic. Thrombosis of the deep cerebral veins may give rise to bilateral thalamic infarcts and result in amnesia, mutism, altered behaviour and delerium.

Other symptoms and complications

Cavernous sinus thrombosis gives rise to a distinct syndrome of localised proptosis, chemosis, painful external ophthalmoplegia and trigeminal (ophthalmic and maxillary) parasthesia. Hypopituitarism is a recognised late complication of this syndrome.

Extensive brain oedema or haemorrhage can lead to tonsillar descent and life threatening brain stem

compression. Pulmonary embolism is a relatively uncommon consequence of CVST, but when it does occur it is also associated with a poor prognosis.[10] Later complications include continued raised intracranial pressure with visual failure, formation of a dural arteriovenous fistula, or epilepsy.

Diagnosis

Imaging

Contrast computed tomography (CT) is often carried out in these patients in the first instance to exclude other pathologies. However, the typical "empty delta" sign, of contrast around the clot in the posterior sagittal sinus, is only seen in about a quarter of cases.[11] The investigation of choice is magnetic resonance (MR) imaging with MR venography (Figure 2). CT contrast venography may be as effective at making the diagnosis,[12] although it is not as sensitive as MRI at detecting the complications and local causes of CVST. Misinterpretation of anatomical variants, such as a unilateral hypoplastic transverse sinus, can be a pitfall in the diagnosis of CVST, and therefore cerebral venography must be interpreted by an experienced radiologist. Invasive angiography is considered the "gold standard" technique for imaging the cerebral veins and sinuses, but the associated risks mean that its use is limited to cases where there is doubt following non-invasive venography.

Lumbar puncture

Lumbar puncture (LP) is likely to show raised CSF pressure, and the CSF may contain increased white cells, red cells and protein. It does not help significantly in making the diagnosis of CVST but may be helpful to exclude other diagnoses such as meningitis or subarachnoid haemorrhage. LP is also useful for the reduction of CSF pressure in patients who present with symptomatic isolated intracranial hypertension.

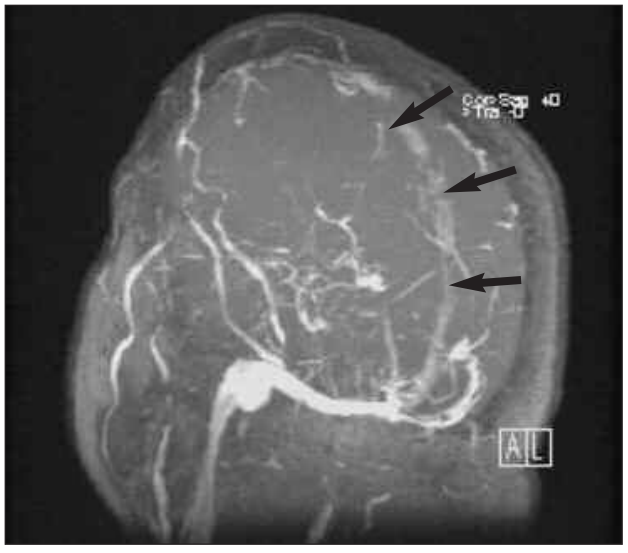

Figure 2. Magnetic resonance venogram in a patient with Sagittal Venous Sinus thrombosis (arrows).

Other investigations

Further investigations are required to identify and exclude possible aetiologies, such as screening for thrombophilias, connective tissue disorders, malignancy or infection (Table 3).

Management

- Monitoring of cardiorespiratory parameters, conscious level, electrolyte balance
- Hydration
- Anticoagulation (initially with dose adjusted IV or low molecular weight heparin)
- Anticonvulsant therapy if seizures occur
- Treatment of any acute underlying condition (e.g. infection)
- Reduction of raised intracranial pressure
- Consider thrombolysis in specialist centres if there is deterioration despite anticoagulation

Investigations

- MRI with MR venography (CT venography may be considered)
- Investigation of underlying cause (including blood tests for infection and inflammatory markers, haematological and thrombophilic disorders, autoimmune inflammatory disorders and chest X-ray)
- Lumbar puncture
- Serial monitoring of visual fields and visual acuities in patients with optic disc swelling

Table 3. Summary of the initial management and investigation of cerebral venous sinus thrombosis.

Treatment

Anticoagulation

It is common practice to anticoagulate patients with CVST to prevent clot propagation and pulmonary embolism. However, there remains a degree of controversy because there are few data from randomised controlled trials and because of the perceived risk of precipitating or worsening an intracranial haemorrhage. A Cochrane systematic review included two randomised trials of anticoagulation in CVST.[13] The first was stopped after only 20 patients because heparin showed an apparent significant benefit over placebo.[14] The second study, which randomised 59 patients to either low molecular weight heparin or placebo, failed to show significant benefit. However, this study importantly demonstrated that there was no significant increased risk of haemorrhage with anticoagulation.[15] Overall, a meta-analysis of the data showed a potential benefit of anticoagulation in CVST with a relative risk reduction in death of 70%, although this did not reach statistical significance.[13]

Based on these findings and other data from non-randomised studies, international guidelines on the management of CVST have now been published. They support the use of anticoagulation, even in patients with intracerebral haemorrhage. It is recommended that treatment should be with either intravenous unfractionated heparin, dose-adjusted to an activated partial thromboplastin time (APTT) of at least double the

baseline, or with subcutaneous low molecular weight heparin. Oral anticoagulation, to a target international normalised ratio (INR) of 2.5, should follow. Anticoagulation is recommended for a total of 3 months if there is a transient risk factor for CVST, 6-12 months if CVST is either idiopathic or due to a mild hereditary thrombophilia, or longer term if it is a second thrombotic event or if there is a severe thrombophilic tendency.[16]

Thrombolysis

There are no randomised controlled data on the efficacy or safety of systemic or local thrombolytic therapy for CVST, and most data comes from case series and individual patients in whom thrombolytic agents were infused directly into the affected sinus. A systematic review of these data concludes that thrombolysis may have a place in patients who have a poor prognosis and who deteriorate despite anticoagulation, but that a randomised controlled trial is required to prove efficacy.[17]

Other supportive treatment

Management is best undertaken in a high dependency or intensive care setting in patients with reduced conscious level and/or evidence of significant brain oedema. Good hydration, monitoring for complications, anticonvulsants for seizure control, treatment of any underlying condition, and management of raised intracranial pressure are all important (Table 3).

For those patients with isolated intracranial hypertension, visual acuity and fields require frequent monitoring for any sign of deterioration. A LP is indicated if the vision is threatened, with CSF removal to obtain a normal closing pressure. In such cases, repeat LPs may be required and it is sensible to postpone oral anticoagulation until CSF pressure is stabilised, because oral anticoagulation will need temporary interruption for each LP. As in IIH, acetazolamide is also frequently used, although there is no evidence specific to CVST to support this. If the patient's vision continues to deteriorate despite acetazolamide and repeat LPs, shunting procedures should be considered.[16]

Outcome and prognosis

Mortality from CVST is approximately 10%,[8] with a further 6% dependent and 40% living a restricted lifestyle at one year.[18] In the Dutch Venous Sinus Thrombosis Study of 59 patients, coma and intracerebral haemorrhage were independent predictors of a poor outcome, whereas those with isolated intracranial hypertension or a delta sign on CT had a good prognosis.[8]

Conclusions

CVST is a life threatening cerebrovascular disorder which affects young adults. It can present in a variety of ways and may mimic a number of other neurological conditions. If the diagnosis is not considered, CVST can easily be missed and it often requires MR or CT venography for confirmation. Management includes hydration, seizure control, reduction of CSF pressure and treatment of underlying causes. Although there are insufficient randomised controlled trial data to be conclusive, carefully administered anticoagulation is recommended and is likely to be safe even in the presence of intracranial haemorrhage.

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