Cerebral venous thrombosis

Peter J Martin, T Peter Enevoldson

The combination of headache and papilloedema (optic disc swelling due to raised intracranial pressure) is a not infrequent reason for a patient's emergency admission to hospital. Such features arise for a variety of reasons (box 1) and initial effort should be directed at excluding intracranial mass lesions or subarachnoid haemorrhage by emergency computed tomography (CT).

A similar clinical picture might also arise due to occlusion of one of the principal intracranial venous pathways – the dural sinuses. Cerebral venous thrombosis (CVT) was first described in the early 19th century and numerous causes or predisposing factors have been described, predominantly in specialist neurology and neurovascular texts. Although uncommon, it is our clinical impression that CVT remains under-recognised. Early diagnosis is important since the condition is potentially fatal but appropriate treatment aids full recovery in the majority of patients. In this overview we describe its diverse presentations and aetiologies, and indicate appropriate investigations and management strategies.

Cerebral venous drainage

The venous drainage of the brain is predominantly via the cerebral veins which communicate with the dural sinuses. Deep cerebral veins communicate with the inferior sagittal and straight sinuses. Superficial cerebral veins (which drain the majority of the cerebral cortex) empty into the superior sagittal sinus which communicates with the transverse sinuses, of which the right is usually dominant. The transverse sinuses communicate with the sigmoid sinuses from which blood drains into the internal jugular veins. Should the superior sagittal sinus be occluded, superior and inferior anastomotic veins provide an alternative route of cortical venous drainage into the cavernous sinuses and transverse sinuses, respectively. With time, further venous collaterals develop and provide a communication between the superficial and deep venous systems.

Cerebrospinal fluid (CSF) pressure is intimately related to cerebral venous pressure since the majority of CSF absorption is via the arachnoid granulations located mainly within the sagittal and other principal dural sinuses. Hence venous sinus obstruction rapidly leads to cerebral venous hypertension, a rise in cerebral blood volume and elevated CSF pressure. This accounts for the early onset of symptoms and signs suggestive of raised intracranial pressure.

Aetiology

Since its description nearly 200 years ago, a plethora of causes and associations of CVT have been described (box 2). In the present era, the causes of CVT can be grouped broadly into endocrine disturbances, haematological/immunological abnormalities, connective tissue and other inflammatory disorders, and neoplastic causes. Infective aetiologies (eg, meningitis, otitis media, subdural empyema) were over-represented in early series and accounted for the apparently high morbidity and mortality (30–50%) of the condition. The mechanism of sinus occlusion is usually either by the development of a prothrombotic state, by direct disturbance of venous flow (eg, compression, low flow states), or by infiltration or inflammation of the sinus wall (eg, the arterioles). Even after full investigation up to 25% of patients with venous sinus occlusion fall into the 'idiopathic' category.

ENDOCRINE CAUSES

Use of the combined oral contraceptive pill is now recognised as a common association both with pure 'benign intracranial hypertension' and venous sinus thrombosis. In the largest series of CVT, the contraceptive pill was the only identified predisposing factor in 8% of cases. In young women presenting with any of the features of CVT a prompt search should be made for evidence of venous occlusion and oral contraception must be promptly withdrawn. In
patients in whom the diagnosis is confirmed we counsel against future use of the contraceptive pill and advise the use of alternative methods.

In developing countries, pregnancy is a common cause of CVT, although symptoms usually occur during the puerperium (box 3), rather than during pregnancy itself. There are insufficient long-term data on recurrence of CVT in future pregnancies but it seems likely that these patients are at high risk and they must be made aware of this.

**HAEMATOLOGICAL/IMMUNOLOGICAL CAUSES**

Diseases such as polycythaemia, sickle cell disease, myeloproliferative disorders and the hyperviscosity syndromes are well known to produce a prothrombotic environment. There is now increasing awareness of disorders of the thrombotic and fibrinolytic pathways and it is apparent that these are commonly associated with thrombotic events, especially in the venous circulation.

The antiphospholipid syndromes are associated with recurrent arterial and venous occlusions (box 4). Patients should be questioned about previous venous thromboses and miscarriages. IgG rather than IgM antiphospholipid antibodies are more likely to be associated with thromboses but it is uncertain whether these antibodies are themselves thrombophilic or whether they are markers of disturbed platelet or endothelial function.

Autosomally inherited deficiencies in the proteins C and S, and antithrombin III are also associated with recurrent thromboses, predominantly venous but also arterial (box 5). Homozygotes suffer neonatal purpura fulminans or severe arterial stroke in childhood. Heterozygotes are more likely to present with venous thromboses in early adulthood although the majority remain asymptomatic.

Proteins C and S are synthesized in the liver and are vitamin-K-dependent anticoagulants. They exist in both active and inactive forms, and inhibit factor Va of the clotting cascade. Protein C abnormalities are the most common inherited thrombophilias and two types (type I and type II) are recognised. The former is associated with a reduction in protein C antigen concentration and activity whereas the latter patients have a reduction in activity with normal antigen levels. In assaying these factors, it is important to perform dynamic testing of activity since apparently normal quantitative analysis may not demonstrate abnormal function. Caution is necessary in anticoagulating these patients since abrupt warfarin administration without adequate heparinisation can lead to paradoxical thrombophilia and fulminant skin necrosis.

**CONNECTIVE TISSUE/INFLAMMATORY CAUSES**

The connective tissue disorders, granulomatous disorders and the arteritides are thought to induce CVT by inflammation or arteritis of the dural sinus walls. Venous sinus thrombosis may rarely be the presenting feature of such conditions, or the underlying cause may only become apparent weeks or months later. More usually, however, CVT will occur in a patient in whom one of the above diagnoses has already been reached.

**NEOPLASTIC CAUSES**

Tumours can induce CVT either by a local, metastatic, or non-metastatic action. The visceral malignancies are associated with CVT in the absence of macroscopic cerebral metastases. Potential mechanisms are the presence of microscopic tumour seedlings within the venous sinuses or a prothrombotic state associated with malignancy. Haematological and lymphoreticular malignancies must also be excluded in a patient with CVT.

Occipital tumours (meningioma, metastases, plasmacytoma and Ewing's sarcoma) have also been noted to impede venous sinus drainage. Occipital meningiomas compressing the sagittal sinus notably precipitate visual failure unless early measures are taken to decompress the optic nerve sheaths (box 6). A CSF shunting procedure or a resection of the tumour may also be necessary.

**Clinical features**

The true incidence of cerebral venous occlusion is unknown but it is almost certainly more common than generally appreciated. With the growing use of noninvasive imaging it is apparent that 25% of patients with benign intracranial hypertension may have underlying CVT. There is a slight female predominance (1.3:1) (probably reflecting oral contraceptive use and pregnancy) with its usual onset in the third or fourth decades.

The presentation of CVT may be acute, subacute, or chronic (box 7). The most consistent features are headache and papilloedema (at least 75% and 50% of cases, respectively). The most common pattern of presentation is with a benign...
intracranial hypertension-like syndrome (headache and papilloedema alone), especially in patients with a history extending over several weeks. The shorter the history, the more likely the presence of focal signs.

Depending on the intracranial pressure a sixth nerve palsy may develop, usually as a false localising sign, but it may also indicate extension of thrombus into the inferior petrosal sinus. If the thrombus extends into the superficial cortical veins there may be transient ischaemia leading to short-lived limb weakness or dysphasia. These fluctuating focal deficits can mimic arterial transient ischaemic attacks but accompanying features (headache, papilloedema, young age of the patient, etc) should provide a guide to their venous origin. Established venous cortical infarction is frequently heralded by seizures and the development of meningism reflects its haemorrhagic nature. Beyond this stage impairment of conscious level is common. The differential diagnosis of CVT is illustrated in box 8.

**Investigation**

The confirmation of CVT no longer requires venous phase intra-arterial angiography, since CT, magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) enable noninvasive diagnosis. Since clinicians are more readily inclined to use the latter investigations, it is becoming apparent that cerebral venous occlusion is more commonplace than originally believed, particularly in patients presenting with benign intracranial hypertension, of whom 25%, may have cerebral venous occlusion. Subsequently, increasingly accurate CT and MR imaging has been developed for this purpose. The confirmation of CVT is illustrated in box 8.

A 36-year-old woman developed frontal headache followed three days later by a sudden, severe occipital pain and vomiting. She described 'black snowflakes' throughout her visual field and suffered a generalised seizure. She was two weeks post-partum following her first pregnancy. The third trimester had been complicated by hypertension. Examination revealed indistinct optic disc margins but no focal signs. Unenhanced CT demonstrated a left occipital haemorrhage. Vertebral artery angiography was normal. The haemorrhage was attributed to her recent hypertension but her headache and visual disturbance persisted. She developed papilloedema but no focal signs. Bilateral haemorrhagic occipital infarcts were apparent on MRI. Venous phase MRA showed occlusion of the left transverse, straight and superior sagittal sinuses. Phenytoin was administered as prophylaxis against further seizures. She was entered into the Dutch-European Cerebral Sinus Thrombosis Trial. Further haematological and immunological testing was normal. Her recovery was complete.

**Case report**

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**Box 3**

**Figure 3** MRI in the axial plane demonstrating thrombus within the transverse sinuses bilaterally (arrows)

**MAGNETIC RESONANCE IMAGING**

The MRI appearances of CVT evolve over time. In the acute phase (within five days) there is absence of the normal venous flow void on T1- and T2-weighted images and the thrombus itself appears isointense and hypointense on these sequences, respectively. Within the next 10 days, hyperintense signals appear within the occluded sinus on T1 and then T2 sequences (figure 2). In continuing obstruction the signal intensity decreases, whilst in cases of recanalisation the venous flow void reappears.

Venous phase MRA is now of sufficient quality to show characteristic filling defects in the principal dural sinuses (figure 3). Unlike conventional angiography, MRA is entirely noninvasive and does not require the administration of contrast. In combination with standard T1- and T2-weighted images it is therefore possible to take angiographic sequences of the venous system as well as making a search for areas of cortical venous infarction which may have been overlooked on CT.

**ANGIOGRAPHY**

Intravenous digital subtraction angiography requires the injection of a large volume of contrast, gives poor definition images of the cerebral venous system and is associated with a high incidence (up to 10%) of systemic reactions to the contrast. It only delineates the principal sinuses and cannot demonstrate cortical venous occlusion.

Intra-arterial angiography (with or without digital subtraction) provides high definition images but is associated with a small risk (<5%) of neurological
Case report

A 34-year-old woman presented with headaches and vomiting for four weeks. Her vision had deteriorated during the four days prior to admission. She had had a miscarriage at eight weeks one year earlier, and a one-week period of swollen painful joints in the feet six months previously.

She was oedematous. Fundoscopy showed haemorrhagic papilloedema. Visual acuity was impaired by counting fingers on the left and hand movements on the right. There was a right relative afferent pupillary defect. Unenhanced CT was normal. At lumbar puncture the CSF pressure was greater than 50 cm with normal protein, glucose and no white cells. It contained 452 red cells, MRI showed a superficial right frontal haemorrhage, and absence of flow void in the superior sagittal sinus. MRA confirmed sagittal and straight sinus thrombosis.

The CSF pressure was controlled by repeated lumbar puncture and dexamethasone. In view of the acute presentation, the progressive visual failure, impairment of conscious level and the extensive sinus thrombosis, anticoagulation was commenced with intravenous heparin followed by warfarin. She responded rapidly. Two weeks later visual acuities were normal and no neurological deficit was apparent. Anticoagulation was continued for six months and she was advised to avoid the contraceptive pill.

The aetiology of the sinus thrombosis was an antiphospholipid antibody/systemic lupus erythematosus overlap syndrome. The erythrocyte sedimentation rate was 61 mm/h; antinuclear factor was positive (1:160); double-stranded DNA was positive (1:208); and IgG and IgM antcardiolipin antibodies were markedly elevated (74 and 53 normal range < 9, < 4, respectively).

Box 4

Complications. Filling defects within the dural sinuses or their complete occlusion is demonstrated on delayed venous phase projections. The technique can also demonstrate the appearance of deep and superficial cortical collateral venous pathways ('corkscrew veins'). It is now being superseded by MRI and MRA, except in the very obese or claustrophobic patient.

LUMBAR PUNCTURE

This procedure carries three purposes. Firstly, analysis of CSF constituents may be required to exclude other pathologies such as meningitis or subarachnoid haemorrhage. CSF analysis, including cytology, can also shed light on the cause of venous thrombosis. The CSF in CVT may be normal, or there may be an increase in protein, white cells and red cells, either alone or in combination. Secondly, measurement of CSF pressure may be of diagnostic value since it is usually markedly elevated (at least 30 cm CSF), and also useful as a baseline should future measurements be required in order to monitor resolution or progression of the disorder. Finally, repeated lumbar puncture to drain CSF is used as a therapeutic manoeuvre when vision is threatened.

Management

REDUCTION OF INTRACRANIAL PRESSURE

Treatment of sagittal sinus thrombosis is influenced by its aetiology and the clinical features. In patients with a pure benign intracranial hypertension-like syndrome diuretics may be sufficient to control the raised intracranial pressure. Steroid administration (dexamethasone) and repeated lumbar puncture are further options. If these measures fail and visual fields and/or acuity deteriorate optic nerve sheath fenestration or lumbar–peritoneal shunting are necessary.

ANTITHROMBOTICS/ANTICOAGULANTS

Anecdotal reports suggest that anticoagulation with intravenous heparin may be of benefit and it seems logical to treat thereafter with warfarin according to the underlying aetiology. There is preliminary evidence to suggest that heparin improves outcome and it is not necessarily contraindicated in the presence of haemorrhagic venous infarction. By limiting further thrombogenesis within the superficial cortical veins, such patients can have a dramatic response to heparinisation. The multicentre Dutch–European Cerebral Sinus Thrombosis Trial (D-ECST) is currently evaluating anticoagulation (with low molecular weight heparin and warfarin). Until results are available it would seem reasonable to reserve anticoagulation for those patients who present early, who have evidence of extensive or progressing thrombosis, whose condition deteriorates despite diuretics and steroids, and those with clinical features of cortical venous involvement (fixed or fluctuating focal deficit, seizures, impaired consciousness).

FIBRINOLYSIS

Theoretically the local administration of thrombolytic agents via venous catheterisation should be of benefit in patients with CVT. Although there are anecdotal reports of successful response, there is insufficient evidence to support their widespread use. Systemic thrombolysis is logistically simpler but concern surrounds intracerebral haemorrhage, particularly in the presence of venous infarction. Trial data is required before thrombolysis can be recommended.

Outcome

Early series of CVT reported mortalities of 30–50% and, left untreated, the condition is potentially life threatening. Recent reports describe mortality rates of 5–30%. The better outcome reflects greater awareness amongst specialists (who are more likely to gather larger series), noninvasive imaging techniques (enabling earlier diagnosis and recognition of milder cases), and the relative decline of infective aetiologies. Amongst survivors, a minority develop a permanent deficit such as focal limb weakness, epilepsy or optic atrophy. When the question of optimum treatment (antithrombotics, anticoagulants and fibrinolytics) is answered the morbidity and mortality associated with CVT should fall further.
Case report

A 26-year-old woman suffered headaches and vomiting for two weeks. There were no neurological signs. A CT scan without contrast revealed a left posterior temporal haemorrhag. Four-vesel intra-arterial angiography was normal. Her headaches worsened and she developed diplopia. She now had bilateral papilloedema, a right upper quadrantanopia, bilateral sixth nerve palsies and a right extensor planter. Repeat CT with contrast showed an 'empty delta' sign. Sagittal sinus thrombosis was confirmed by MRA. Axial MRI also showed thrombosis of the left transverse sinus and revealed the initial left temporal haemorrhage to be a haemorrhagic infarct.

Treatment comprised dexamethasone with a thiazide diuretic. However, the patient deteriorated, developing pyramidal weakness of the right-sided limbs, a dysphasia and seizures. This suggested thrombus extension into the superficial cortical veins. She was anticoagulated with intravenous heparin and then warfarin. Recovery was full.

Further studies revealed abnormal activated protein C activity. The initial clotting profile antithrombin III and protein S activity were normal. Protein C antigen was 196% (high) with a reduced protein C activity (35%) and a low protein C co-factor.

Case report

A 46-year-old man presented with two generalised convulsions. He had undergone renal transplantation four years previously. Neurological examination was normal. MRI showed a lesion in the left occipital lobe with surrounding oedema suggestive of a meningioma.

Two weeks later he developed headache, blurred vision and bilateral papilloedema. His visual acuity was 6/9 in both eyes. Venous phase intra-arterial angiography and MRA showed the occipital lesion to be partially obstructing the superior sagittal sinus. His visual acuity deteriorated to finger counting on the right and perception of light on the left, and his CSF pressure was 70 cm at lumbar puncture. There was no improvement in his vision despite repeated lumbar punctures. He underwent bilateral optic nerve sheath fenestration and ventriculo-peritoneal shunting. His visual acuity improved to 6/24 and 6/60 in the right and left eyes, respectively.

Box 6

CVT: clinical features

- headache
- papilloedema
- sixth nerve palsy (as a false localising sign, or inferior petrosal sinus thrombosis)
- fluctuating or fixed motor or sensory signs
- dysphasia
- seizures
- impairment or fluctuation of consciousness
- third, fourth and sixth nerve palsies (in cavernous sinus thrombosis)

Box 7

CVT: differential diagnosis

- 'pure' benign intracranial hypertension
- migraine
- meningitis
- encephalitis
- cerebral infarction (arterial)
- intracerebral haemorrhage
- cerebral abscess
- primary or secondary tumour
- eclampsia of pregnancy

Box 8
Cerebral venous thrombosis.

P. J. Martin and T. P. Enevoldson

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