Cerebral venous and dural sinus thrombosis

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Although our brain has many more veins than arteries, thrombosis of the cerebral veins and dural venous sinuses (cerebral venous thrombosis, or CVT) is much less frequent than arterial occlusion. It is also more difficult to diagnose because of the wide spectrum of clinical presentation and the need for magnetic resonance imaging (MRI) and/or catheter angiography to confirm the diagnosis. Indeed, the diagnosis can be delayed days or even weeks after the onset of neurological symptoms, and after the patient has been seen by several physicians (Ferro *et al.* 2001). But CVT is not just a neurological curiosity, to be managed only by academic neurologists. It can complicate the course of several systemic diseases and also pregnancy. Therefore, it should be of concern to internists, haematologists, oncologists, obstetricians, and emergency and intensive care physicians.

EPIDEMIOLOGY
The annual incidence in adults is 0.22/100 000 (Ferro *et al.* 2001) so about 5–10 patients with CVT are likely to be admitted each year to a tertiary care centre. CVT is most frequent in infants and neonates (DeVeber *et al.* 2001), and in patients between 20 and 40 years of age. Women are affected three times more often than men.

CLINICAL FEATURES
The presentation of CVT can be acute, subacute or chronic. The presenting symptoms are grouped into four major syndromes (Bousser *et al.* 1997):
- isolated intracranial hypertension – headache, visual obscurations, vomiting, papilloedema ± sixth nerve palsy (Biousse *et al.* 1999);
- focal syndrome – focal or generalized seizure and/or a focal deficit such as mono- or hemi-paresis or aphasia;
- encephalopathy – multifocal or bilateral focal deficits and/or seizures, mental changes such as abulia or delirium, and in severe forms stupor or coma;
- cavernous sinus syndrome – oculomotor palsies ± fifth cranial nerve pain or sensory loss ± proptosis or chemosis.

Other less frequent presentations are pulsatile tinnitus and cranial nerve palsies (Kuehnen *et al.* 1998).

The most frequent symptom is headache. This may be severe and increase when the patient lies down or performs a Valsalva manoeuvre, but often the headaches do not have these features. Papilloedema is found in one third of patients and in a few visual acuity is already decreased before admission.

CONFIRMATION OF THE DIAGNOSIS

In clinical practice, computed tomography (CT) of the brain is usually the first imaging technique in patients with headache, seizures or disturbed consciousness. In CVT, the CT may be normal or show intracerebral haemorrhages, infarcts or focal or diffuse brain oedema. In a few patients there may be some hints to the diagnosis of CVT, such as hyperdensity of a thrombosed sinus (Fig. 1). And, after contrast injection, an occluded torcula often appears as an 'empty' triangle (the empty delta sign). Increased venous collateral circulation can produce intense contrast enhancement of the falx and tentorium. Lesions visible on admission CT may disappear (vanishing infarcts) or new lesions may appear. Unfortunately, the CT features, even the empty delta sign, are not specific, and CT cross sectional imaging alone cannot confirm the diagnosis of CVT. But, where available, CT venography can be performed rapidly and this delineates the intracerebral venous circulation with high sensitivity (Wetzel *et al.* 1999).

MRI/MR venography is usually required to confirm the diagnosis of CVT. MR has the advantage of demonstrating any parenchymal lesions, as well as the thrombus and the non-filling vessel (Figs 2 and 3). Diffusion/perfusion MR shows that the parenchymal lesions are more often due to vasogenic than cytotoxic oedema or infarction (Keller *et al.* 1999). Intra-arterial catheter angiography with venous views (Fig. 4) is reserved for cases where the diagnosis of CVT is doubtful on MRI and MR venography. However, catheter angiography cannot distinguish between venous
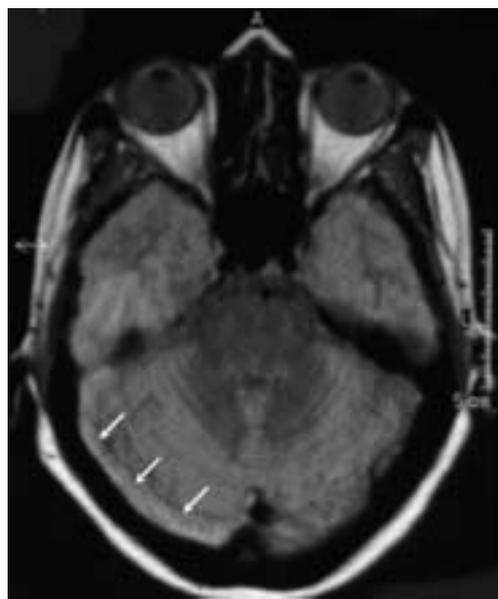
Figure 2 T2-weighted MR sequence. Hyperintensity of the occluded lateral sinus (arrows).

Figure 1 Thrombosed right lateral sinus (arrows) appearing as a spontaneous hyperdensity on an unenhanced CT brain scan of a 40-year-old woman with headache and vomiting.

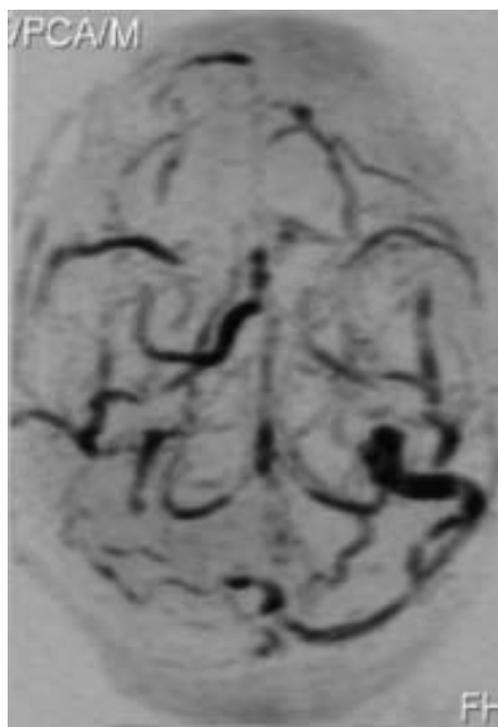**Figure 3** MR-angiogram. The occluded right lateral sinus and the saggital sinus are not displayed. Cortical veins are enlarged.
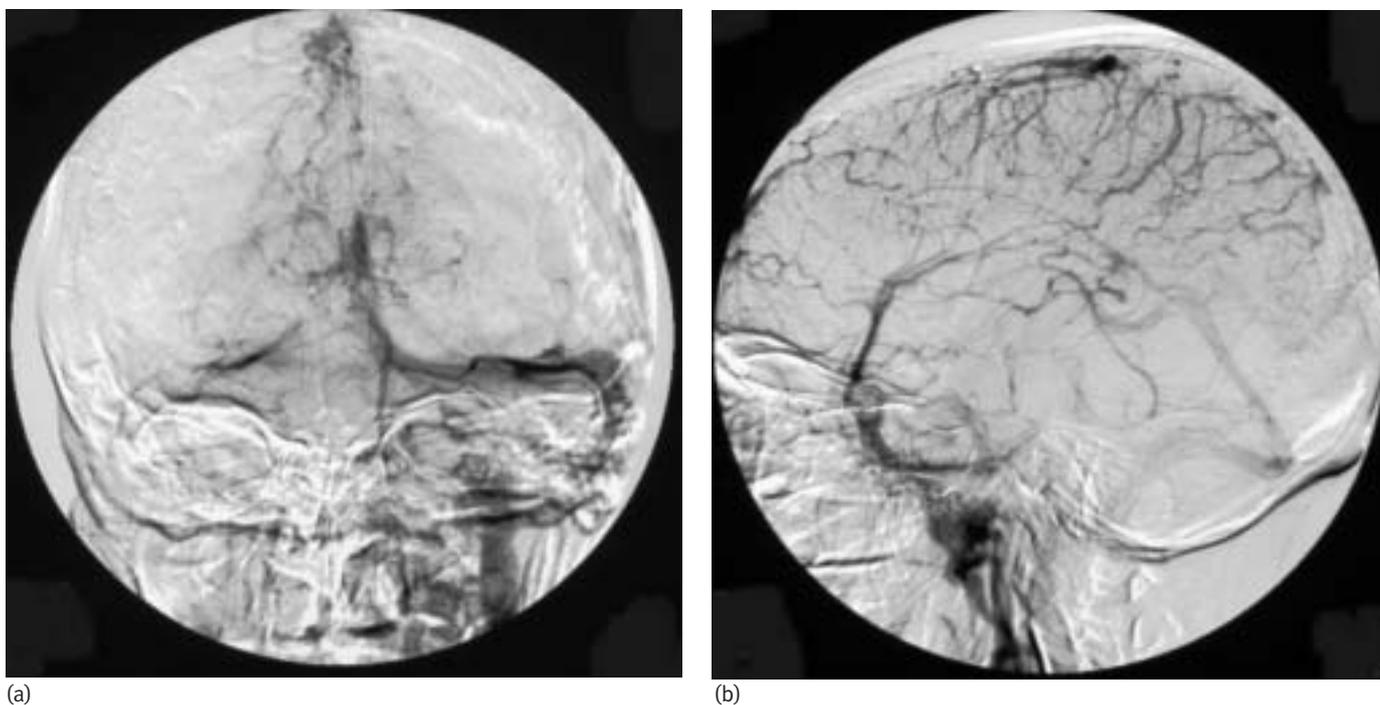
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Figure 4 Intra-arterial digital venography. Occlusion of the right lateral sinus and saggital sinus with prominent collateral veins

thrombosis and hypoplasia of the anterior one third of the saggital sinus, or asymmetry or atresia of one of the transverse sinuses.

The imaging diagnosis of CVT is not always easy and interobserver agreement is not perfect (De Bruijn *et al.* 1998). The radiologist has to compare the MR images of the brain parenchyma with the patency and intensity of the signal of the sinuses in different MR sequences. The diagnosis may be especially difficult in the first few days of the illness because the fresh thrombus is hypointense on T2 and isointense on T1 sequences. After the first four days the thrombus becomes hyperintense on both T1 and T2 and is easier to identify. Clinicians *must* inform the radiologist that they want to exclude CVT and ask specifically for venography to be performed.

Lumbar puncture may be needed to rule out meningitis and to confirm raised intracranial pressure in patients presenting with isolated intracranial hypertension. However, it should only be performed after excluding intracerebral haemorrhage or large infarcts with CT, and before any anticoagulation is initiated because of the risk of spinal haematoma in anticoagulated patients.

PREDISPOSING AND PRECIPITATING CONDITIONS

The development of an acute or subacute neurological syndrome in certain clinical settings should make the clinician consider CVT as a possible diagnosis: women taking oral contraceptives; pregnancy and the puerperium; intracranial, ear or sinus infections; cancer; and haematological conditions (Table 1). The risk of venous thrombosis in an individual varies throughout life, increasing with episodic conditions such as infections, surgery, pregnancy and the puerperium, or the use of drugs such as oral contraceptives. The individual risk is increased by genetic prothrombotic conditions such as protein C, S and antithrombin III deficits, hyperhomocysteinemia, and prothrombotic mutations like factor V Leiden or prothrombin 20210 GA (Martinelli *et al.* 1998; Biousse *et al.* 1998). Therefore, in an individual patient, more than one predisposing condition may be present rather than a single cause, for example a woman with factor V Leiden *and* in the puerperium.

PROGNOSIS

A few patients (about 4%) with CVT die in the acute phase due to increased intracranial pressure and transtentorial herniation, pulmonary embolism, grand mal status, or the underlying condition. The majority make a complete recovery although some patients are left with visual, motor, language, cognitive or behavioural sequelae. But only a minority becomes dependent after CVT. Patients presenting with isolated intracranial hypertension have a much lower risk of neurological deterioration (their greatest risk is visual loss) and

a better prognosis than those with other presentations. Some variables have been associated with a less favourable outcome and are listed in Table 2 (Rondepierre *et al.* 1995; Bousser *et al.* 1999; Barinagarrementeria *et al.* 1992; Preter *et al.* 1996; De Bruijn *et al.* 2000; Ferro *et al.* 2002).

CVT recurrence is extremely rare, but deep venous thrombosis of the extremities may occur, especially in patients with prothrombotic conditions. Pregnancy seems safe in patients with previous CVT. Late visual loss is rare. Some patients have persisting severe headaches. Seizures are a hazard (10%) in the years following CVT, even in patients who did not have seizures in the acute phase. Patients with seizures in the acute phase, or with intracerebral haemorrhage, have a higher long-term risk of seizures (Ferro *et al.* 2003). Dural arteriovenous fistulae are a rare late complication.

TREATMENT

See Fig. 5. The treatment of CVT includes managing the predisposing/precipitating conditions, antithrombotics, lowering intracranial pressure and symptomatic treatment for seizures, headaches and visual failure. Given the rarity of CVT, it is not surprising that there is little evidence from randomized trials to help guide individual patient management.

Management of predisposing and precipitating conditions

This fundamental step is relatively easy if the patient is known to have a predisposing condition. But this can be delayed by the diversity of possible causes and the difficulty in confirming one or more of them. If the patient is febrile or has evidence of infection, appropriate antibiotics are indicated, first obtaining specimens for culture. If there is sinus or ear infection amoxicillin/ clavulanate or cefuroxime is recommended initially, but occasionally surgical treatment is required. Septic sinus thrombosis requires treatment with a combination of a third-generation cephalosporin and metronidazole. For septic cavernous sinus thrombosis a penicillinase-resistant antibiotic should be added.

Antithrombotic treatment

A meta-analysis of two small trials (Einhäupl *et al.* 1991; De Bruijn *et al.* 1999) demonstrated a 16% relative risk reduction of death or dependency on anticoagulants (IV heparin or sc.nadroparin) compared with placebo in the acute phase of CVT (De Bruijn *et al.* 1999).

Table 1 Predisposing and precipitating conditions for cerebral venous and dural sinus thrombosis

Predisposing conditions
Genetic prothrombotic states
Protein C, S or antithrombin deficits
Factor V Leiden, prothrombin 20210 GA
methylenetetrahydrofolate – reductase (MTHFR) mutations
Acquired prothrombotic states
Antiphospholipid antibody syndrome
Vasculitis
Lupus, Behçet's disease, Wegener's granulomatosis
Other inflammatory diseases
Inflammatory bowel disease, sarcoidosis
Malignancy
Any cancer, including CNS tumours
Haematological nonmalignant diseases
Polycythaemia, thrombocytopenia, severe anaemia
Thyroid disorders
Dural arteriovenous fistulae
Precipitating factors
Infections
Brain, meninges, ears, sinuses, etc.
Pregnancy, puerperium
Mechanical
Neurosurgery, recent head trauma, lumbar puncture, jugular catheter
Surgery
Dehydration
Illicit drugs
Oral contraceptives
Other drugs
L-asparaginase, other cytotoxic drugs, tamoxifen, steroids, androgens, oestrogen replacement therapy

Table 2 Variables associated with increased risk of a poor outcome in cerebral venous and dural sinus thrombosis

older age
mental status disorder (abulia, delirium), coma
thrombosis of the deep venous system
intracerebral haemorrhage
central nervous system infection
cancer

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                              ACUTE CVT
                              Confirmed by
                            MR and/or catheter
                              angiography

  TREAT              ANTITHROMBOTIC        REDUCE                        SYMPTOMATIC
  PREDISPOSING/      THERAPY               INTRACRANIAL                  TREATMENT
  PRECIPITATING                            PRESSURE
  CONDITIONS

1st line             IV HEPARIN           LUMBAR PUNCTURE      SEIZURES          HEADACHE
                     SC NADROPARIN        MANNITOL             IV valproate      analgesics
                                          DIURETICS            IV phosphenytoin  reduce intracranial pressure
                                          STEROIDS (?)                           lumbo-peritoneal shunt

Not improving        LOCAL                SEDATION                              VISUAL FAILURE
or deteriorating     THROMBOLYSIS         VENTILATION                           reduce intracranial pressure
on 1st line treatments                    CRANIECTOMY                           lumbo-peritonea shunt
                                                                                optic nerve fenestration
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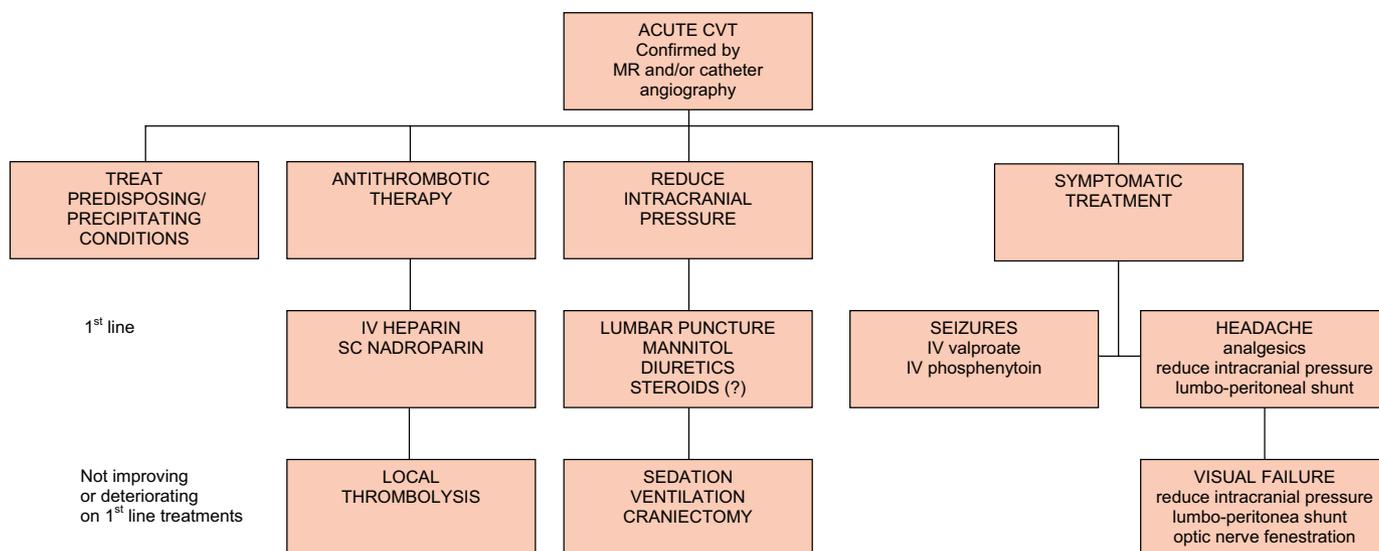
Figure 5 Treatment of cerebral venous and dural sinus thrombosis (CVT).

Patients with a good prognosis, such as those presenting with isolated intracranial hypertension, also benefit from anticoagulation (Biousse *et al.* 1999). Anticoagulation of CVT is safe (Einhäupl *et al.* 1991; De Bruijn *et al.* 1999), even in patients with intracerebral haemorrhage (Ferro *et al.* 2001). Anticoagulation is also useful in the prevention of pulmonary embolism, which is a serious but fortunately rare direct complication of CVT involving the lateral sinus or jugular vein (Diaz *et al.* 1992). Therefore, anticoagulation with IV heparin (1000 U/ h, APPT 1.5–2.5x control, for no more than 7 days) or SC nadroparin (0.6 cc, sc, every 12 h, for to 1–3 weeks, depending on the severity of the clinical condition) followed by warfarin with a target INR between 2 and 3 is recommended for all patients with CVT, regardless of the clinical presentation and imaging features. Warfarin should be maintained for 6 months, or longer (eventually for life) in patients with genetic or acquired prothrombotic conditions. Antiplatelet drugs are an alternative for patients with contraindications to anticoagulants.

A systematic review of published case and case-series (Canhão *et al.* 2003) suggests that local (into the thrombosed sinus) thrombolytic therapy is safe and may be useful in CVT patients with a bad prognosis (Horowitz *et al.* 1995; Frey *et al.* 1999). The concomitant use of mechanical disruption of the thrombus with a rheolytic catheter has also been attempted (Scarrow *et al.* 1999). Until the efficacy and safety of local thrombolysis is assessed in a randomized trial comparing it with conventional therapy, its use should be restricted to patients who are not improving or who deteriorate despite anticoagulation and adequate management of intracranial hypertension.

Treatment of intracranial hypertension

Treatment of intracranial hypertension is a key intervention to improve patients symptomatically and to prevent death in severe cases of CVT: osmotherapy (mannitol), diuretics (acetazolamide or furosemide) or steroids. Patients in stupor or coma may need sedation, artificial ventilation and intracranial pressure monitoring. External ventricular drainage and craniectomy are life-saving procedures in desperate cases (Stefini *et al.* 1999). Symptomatic patients with persistent increased intracranial hypertension are candidates for a lumbo-peritoneal shunt. Repeated lumbar puncture to reduce intracranial pressure should be reserved for patients presenting with isolated intracranial hypertension and papilloedema along with impending visual loss and severe headache.

Symptomatic treatment

Patients with seizures at onset and those who develop seizures in the acute phase should be given anti-epileptic drugs. Patients with risk factors for late seizures – seizures in the acute phase and intracranial haemorrhage (Ferro *et al.* 2003) – should receive anti-epileptics for a year. If they remain seizure free, the anti-epileptics can be gradually discontinued.

CONCLUSIONS

- Thrombosis of the cerebral veins and dural venous sinuses has a wide spectrum of clinical presentation. Confirmation of the diagnosis usually requires magnetic resonance imaging and/or catheter angiography.
- The development of an acute or subacute neurological syndrome in certain clinical settings, such as: women taking oral contraceptives; pregnancy and the puerperium; intracranial, ear or sinus infections; cancer and haematological conditions, should make the clinician consider CVT as a possible diagnosis.
- Nonetheless, the diagnosis of CVT is often delayed days or even weeks after the onset of neurological symptoms.
- The paradox in CVT is on the one hand there are so many patients with non-specific symptoms (headache, seizures, etc.) that *might* be due to CVT, and on the other hand the need for expensive and not widely available technologies such as MR to make the diagnosis in the very few who do have CVT.
- Treatment of the underlying condition, anticoagulants and reducing intracranial pressure are the three fundamental therapeutic interventions.

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