Postgrad Med J 2000;**76**:12–15 © The Fellowship of Postgraduate Medicine, 2000

Classic diseases revisited

Cerebral venous sinus thrombosis

Holger Allroggen, Richard J Abbott

Summary
Cerebral venous sinus thrombosis is a challenging condition because of its variability of clinical symptoms and signs. It is very often unrecognised at initial presentation. All age groups can be affected. Large sinuses such as the superior sagittal sinus are most frequently involved. Extensive collateral circulation within the cerebral venous system allows for a significant degree of compensation in the early stages of thrombus formation. Systemic inflammatory diseases and inherited as well as acquired coagulation disorders are frequent causes, although in up to 30% of cases no underlying cause can be identified. The oral contraceptive pill appears to be an important additional risk factor. The spectrum of clinical presentations ranges from headache with papilloedema to focal deficit, seizures and coma. Magnetic resonance imaging with venography is the investigation of choice; computed tomography alone will miss a significant number of cases. It has now been conclusively shown that intravenous heparin is the first-line treatment for cerebral venous sinus thrombosis because of its efficacy, safety and feasability. Local thrombolysis may be indicated in cases of deterioration, despite adequate heparinisation. This should be followed by oral anticoagulation for 3-6 months. The prognosis of cerebral venous sinus thrombosis is generally favourable. A high index of clinical suspicion is needed to diagnose this uncommon condition so that appropriate treatment can be initiated.

Keywords: cerebral venous sinus thrombosis

Department of Neurology, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK
H Allroggen
R J Abbott

Correspondence to H Allroggen, Queen Elizabeth Neuroscience Centre, Department of Neurology, University Hospital Birmingham, Edgbaston, Birmingham B15 2TH, UK

Submitted 22 March 1999
Accepted 26 July 1999

Cerebral venous sinus thrombosis (CVST) is an uncommon condition which over the past 5 to 10 years has been diagnosed more frequently due to greater awareness and the availability of better non-invasive diagnostic techniques. Because of the generally good prognosis and variable clinical signs, many cases remain clinically undetected. CVST is slightly more common in women, particularly in the age group of 20 to 35, due to pregnancy, puerperium and oral contraceptive use. Mean age in most larger studies was between 37 and 38 years though all ages can be affected.[1 2] The clinical spectrum, however, is wide and recognition remains a challenge for the clinician.

Pathology

Blood from the brain drains through small cerebral veins into larger veins such as the vein of Galen. These bigger veins empty into dural sinuses which themselves are drained mostly by the internal jugular veins. The venous territories are less well defined than are arterial territories due to the presence of extensive anastomoses between cortical veins. These allow the development of collateral circulation in the event of an occlusion. The main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%). In about one-third of cases more than one sinus is affected.[3] In a further 30–40% both sinuses and cerebral or cerebellar veins are involved.[1 3]

Pathophysiologically, there are important differences between arterial and venous thrombosis. CVST has been described as a continuing process in which the balance of prothrombotic and thrombolytic processes is disturbed, leading to progression of the venous thrombus with time.[2] This slow growth of the thrombus and the good collateralisation of the venous vessels probably explain the usually gradual onset of symptoms, frequently over weeks and months.[1 2] Sudden onset, however, has been described.[4] From the large number of patients with complete reversibility of their neurological deficit, it can be inferred that there must be a large area of only transiently and reversibly disturbed cerebral tissue. Recovery appears to be unrelated to the duration of symptoms and signs.[2 3] Haemorrhagic infarction occurs in approximately 10–50% of cases, principally affecting the cortex and adjacent white matter.[2 5–7] This is thought to be primarily due to elevated venous and capillary pressure caused by the persistence of thrombosis.[2]

Aetiology

Predisposing factors can be identified in up to 80% of patients.[8] Numerous conditions can cause or predispose to CVST and often more than one cause will be found in an individual patient (box 1). A principal distinction can be made between infective and non-infective causes. Infective causes have declined and were responsible for only 8% of cases in recent series,[1 2] typically affecting the cavernous sinus following staphylococcal infection of the face.[1] Amongst the non-infective causes, systemic conditions such as connective tissue diseases, other granulomatous or inflammatory disorders and malignancies are most common.[1] In the Middle East, Behcet's disease may be responsible for up to 25% of cases.[9]

In young women, CVST occurs more frequently during the puerperium than during pregnancy.[1] Oral contraceptives and various coagulation disorders have frequently been implicated recently. A Dutch study found an age-adjusted odds ratio of 13 for oral contraceptive use and risk of CVST.[10] Hereditary prothrombotic conditions such as Factor V Leiden (leading to increased resistance to activated protein C), deficiency of proteins C and S and antithrombin III as well as prothrombin gene mutations may account for 10–15% of cases of CVST.[11 12] The risk of a carrier of any of these prothrombotic conditions developing CVST is increased by the coexistence of other predisposing factors. For example, the odds ratio for women using oral contraceptives and also carrying a prothrombotic defect was calculated at 30 relative to women who had neither

Recognised causes and predisposing factors of cerebral venous sinus thrombosis.

Infective causes
- penetrating head injury
- intracranial infection
- regional infection
- sepsis and systemic infection

Non-infective causes
- head injury
- neurosurgery
- stroke and haemorrhage
- space occupying lesions
- infusions via central venous catheter
- surgery with immobilisation
- hormonal and endocrine causes
- cardiac disease
- malignancies
- red blood cell disorders
- thrombocythaemia
- coagulation disorders (acquired or hereditary)
- severe dehydration
- inflammatory bowel disease
- connective tissue diseases
- Behcet's disease
- sarcoidosis
- nephrotic syndrome
- drugs (L-asparaginase, epsilonaminocaproic acid, ecstasy)

Box 1

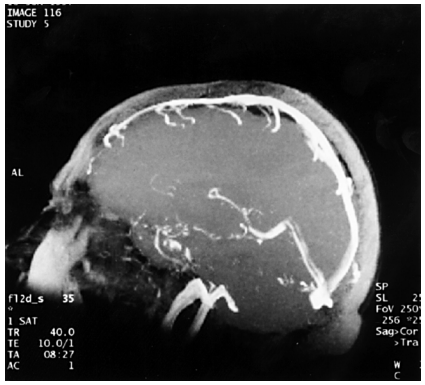

Figure 1 Normal MRV (sagittal view) showing normal flow in both the superior sagittal sinus and straight sinus

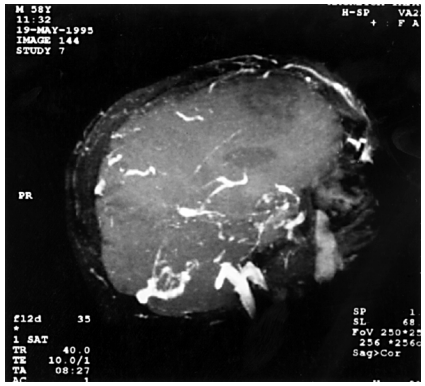

Figure 2 MRV (sagittal view) demonstrating extensive thrombosis of the superior sagittal sinus and straight sinus with some visible small collateral veins

risk factor.[10] It is, therefore, advisable to discourage women who have a history of venous thrombotic disease from using oral contraceptives, especially if they are carriers of a prothrombotic disorder.[10] Whether young women who wish to take oral contraceptives should be screened for these disorders remains controversial.[13] In 20–30% of cases of CVST extensive search reveals no underlying cause,[1 14] indicating the need for close follow-up.

Clinical presentation

CVST presents with a wide spectrum of symptoms and signs. Headache is the presenting symptom in 70–90% of cases.[1 2 5] Focal deficits such as hemiparesis and hemisensory disturbance, seizures, impairment of level of consciousness and papilloedema occur in one-third to three-quarters of cases.[1 5] The onset may be acute, subacute or insidious, most patients presenting with symptoms which have evolved over days or weeks.[1] There are several typical clinical constellations[2 3]: 18–38% of cases present with a syndrome resembling benign intracranial hypertension with headache, papilloedema and visual disturbances; up to 75% of cases are characterised by a focal neurological deficit and headache; a third group of between 30% and 50% may present with seizures often followed by a Todd's paresis. Rare but classical clinical pictures are that of superior sagittal sinus thrombosis (4%) with bilateral or alternating deficits and/or seizures and cavernous sinus thrombosis (3%) with chemosis, proptosis and painful ophthalmoplegia.[1] An even less frequent presentation is a rapidly progressive illness with deepening coma, headache, nausea and pyramidal signs, due to extensive involvement of the deep cerebral veins.[15] Thunderclap headache with neck stiffness mimicking subarachnoid haemorrhage has been described.[4] In the early stages there may be cortical vein thrombosis without sinus thrombosis, the latter developing only later due to progression of the thrombotic process. There is no well-defined clinical syndrome to suggest this, although the rapid onset of focal deficit and/or seizures is thought to be typical of this situation.[1] There is strong overlap between all these outlined groups and patients may progress from one to the other in the course of their illness.

Diagnosis

Investigations should focus on establishing the diagnosis and searching for underlying causes. Magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) have largely replaced invasive cerebral angiography and conventional computed tomography (CT). The latter will, however, often remain the first imaging modality to be used simply due to availability and also to exclude other conditions such as intracerebral haemorrhage or abscess. The 'empty delta sign' on CT, reflecting the opacification of collateral veins in the wall of the superior sagittal sinus after contrast injection is present in only 10–20% of cases.[1] CT is entirely normal in 10–20% of cases with proven CVST.[1] MRI combined with MRV is reliable as the sole examination for this condition.[16 17] It can show the consequences of thrombosis such as cerebral oedema, infarction and haemorrhage as well as the anatomy of the disturbed venous circulation (figures 1–4). There are, however, pitfalls of this technique which may, in doubtful cases, make cerebral angiography necessary.[1 7 16] One of the common problems is the absence or hypoplasia of the anterior portion of the superior sagittal sinus, a normal variant that can simulate thrombosis on MRV. Also, contrast enhancement along the edge of the thrombus can be mistaken for normal contrast material accumulating within a patient's sinus.[7] More recently, CT venography has been shown in at least one series[18] to be superior to MRV in visualising sinuses or smaller cerebral veins or cortical veins with low flow. This technique is not used routinely at present.

Examination of the cerebrospinal fluid (CSF) does not necessarily help in establishing the diagnosis as there are no pathognomonic features. Abnormalities are found in up to 84% of cases and include raised CSF pressure, increased protein content, the presence of red blood cells and pleocytosis.[5] Nevertheless, examination of the CSF remains important in the appropriate clinical context to rule out meningitis or subarachnoid haemorrhage before the diagnosis of CVST has been established. Its other value is in patients who are thought to have benign intracranial hypertension where the presence of any abnormal findings in the CSF should point towards CVST as the underlying cause of raised pressure.

All other investigations are directed towards demonstrating the underlying cause. Clinically obvious cases such as local infection or head injury may be self evident whereas extensive investigations are needed in the 'idiopathic' cases. Suspicion of malignancies or connective tissue diseases should be confirmed with appropriate tests such as chest X-ray or other imaging, inflammatory

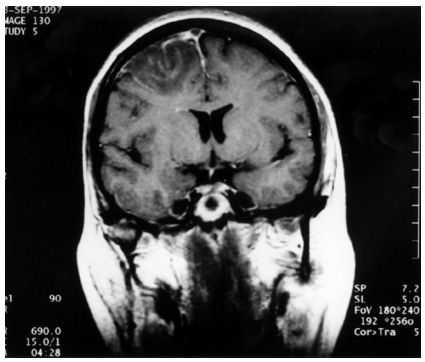

Figure 3 MRI showing a venous infarct in the parasagittal area on the right and enhancement around the thrombus in the superior sagittal sinus (T_1-weighted image with contrast, coronal view)

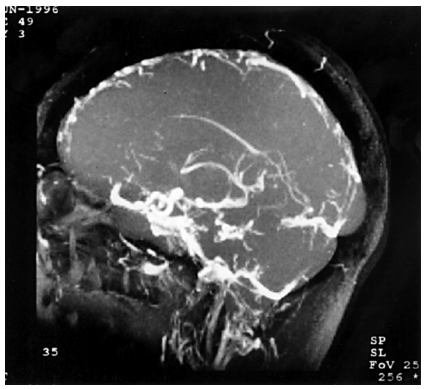

Figure 4 MRV (sagittal view) of partially recanalized thrombosis with frayed appearance of the superior sagittal sinus and multiple collateral veins.

Summary points

- CVST is an uncommon disorder
- it can affect all age groups but young and middle aged women appear at particular risk.
- there is extensive collateral circulation in the cerebral venous system
- the superior sagittal and lateral sinuses are most frequently affected, often in combination with other sinuses or veins
- haemorrhagic infarction is common
- systemic inflammatory diseases and coagulation disorders (with or without use of oral contraceptives) are frequent causes
- the spectrum of clinical presentation is extremely wide
- headache, papilloedema, focal deficits, seizures and impairment of consciousness affect between one-third and three-quarters of patients
- the diagnostic test of choice is MRI with MR venography
- search for acquired or hereditary coagulation disorders is mandatory, particularly in cases with positive medical or family history of thrombotic episodes and where no other cause has been found
- treatment with intravenous heparin followed by oral anticoagulants should be given to all patients
- prognosis is generally favourable

Box 2

markers, autoantibodies or tissue biopsies. Coagulation studies are important particularly in patients with a family or past medical history of thrombotic episodes in addition to the unexplained cases. The investigations should include a search for the Factor V Leiden mutation if resistance to activated protein C is abnormal, activities of proteins C and S and antithrombin III, plasminogen, fibrinogen and anticardiolipin antibodies.[11] All these investigations should probably be performed twice, ie, before starting anticoagulation and 6 months later after finishing treatment. Many of the above parameters can be transiently influenced by a number of factors, including antithrombotic treatment, pregnancy, oral contraceptives and acute thrombosis.[11]

Treatment

There are few therapeutic trials in CVST. The antithrombotic treatment modalities include heparin, thrombolysis and oral anticoagulants.

The safety of heparin treatment has been shown in two larger[1 5] and many smaller series and case reports. The benefits of heparin have been demonstrated in a randomised and placebo-controlled trial of 20 patients.[19] There was a significant difference in favour of intravenous heparin, with a target partial thromboplastin time of 80–100 s, with respect to neurological recovery and mortality. Eight patients in the heparin group but only one in the placebo group recovered fully. The authors also retrospectively analysed 102 patients with CVST, and showed that intravenous heparin was even beneficial in those patients who had an intracranial haemorrhage prior to starting treatment. In a further placebo-controlled trial,[20] 60 patients were randomised to either low-molecular-weight heparin followed by warfarin, or placebo. There were no statistically significant advantages in favour of heparin. Complete recovery was observed in 20% of anticoagulated patients and in 28% of controls; a poor outcome at 12 weeks was documented in 13% of heparin-treated patients but in 21% of control subjects. Even the 15 patients with haemorrhagic lesions did not worsen with anticoagulation.

There have been several case reports and four larger series of thrombolysis via selective catheterisation of the occluded sinus.[21–24] In the first study,[21] 12 patients, of whom four had haemorrhagic infarcts, were pre-treated with intravenous heparin and then given urokinase boluses followed by continuous infusion via a transfemoral venous catheter into the occluded sinus. There was no major therapeutic morbidity, one patient died of pulmonary embolism but 10 patients had good or excellent clinical outcome (one inadequate follow-up). Functional sinus patency was achieved in 11 of 12 patients. Treatment duration was between 12 and 84 hours with repeated venograms and arteriograms performed at 24-hour intervals. In the second series,[22] seven patients who deteriorated despite heparin were thrombolysed with urokinase via selective transfemoral catheterisation. None of the patients had a documented haemorrhage prior to treatment. There were again no major complications and all patients either fully recovered or improved. Sinus patency was achieved in all patients following thrombolysis for between 88 and 244 hours. In the third series,[23] nine patients were given recombinant tissue plasminogen activator with concomitant intravenous heparin via the transfemoral route. Complete flow restoration was achieved in all patients within, on average, 18 hours. All cases completely recovered. The latest study[24] used the same agent and achieved complete flow restoration in six of 12 patients. Complete recovery occurred in seven of 12 cases. Two patients worsened because of increased intracerebral haemorhage. The need for enormous organisational efforts and expertise limit this intervention to specialised centres. Furthermore, it is still extremely difficult to assess the benefit-to-risk ratio of this treatment. There is no direct comparative trial between heparin and thrombolysis.

Most investigators suggest oral anticoagulants following the treatment of the acute phase for 3–6 months, except when there is a known prothrombotic condition in which treatment may have to be life-long.[1 3 25] Other symptomatic treatments such as antibiotics, anticonvulsants, anti-emetics and analgesia will depend on the circumstances. Whether anti-epileptic treatment should be given to all patients or only to those who present with or develop seizures is controversial.[3 25] Special interventions to reduce significantly raised intracranial pressure, for example when vision is threatened, include acetazolamide, steroids, repeated lumbar punctures, mannitol, shunt procedures and barbiturate-induced coma.

In summary, intravenous heparin should be the first-line treatment, even in the presence of haemorrhagic infarction, provided there are no general contraindications to its use.[1 25 26] If the patient deteriorates despite adequate heparinisation or presents moribund with coma, selective catheter-guided local thrombolysis may be

Questions

1 Which patient group is at a particular risk of developing CVST?
2 What is the important anatomical difference between the cerebral venous and arterial circulation?
3 Which causes or predisposing factors have recently been recognised more frequently?
4 What are the most frequent symptoms and signs at presentation?
5 What is the investigation of choice for confirming CVST?
6 What should be the first line of treatment for patients with CVST?
7 Are there any clinical factors that indicate prognosis?

The answers can be found on p 64 of this issue.

an option,[25 26] in spite of the increased haemorrhagic risk. This should be followed by 3–6 months of oral anticoagulation.

Prognosis

Between 57 and 86% of patients have complete functional recovery.[2 20 27] Mortality ranks between 5.5% and 18% in recent series.[1 2 20] Even though there appears to be no clear correlation between disease severity and outcome,[1] several factors are associated with a poorer prognosis. These are, most importantly,[8] infancy and advanced age, rapid onset with coma and focal deficits, and thrombosis affecting largely the deep venous system. The underlying condition, particularly sepsis, malignancy, and paroxysmal nocturnal haemoglobinuria adversely affect outcome.[8] Twelve per cent of patients suffer a recurrence of CVST and 14% a different form of venous thrombosis.[27] Seizures rarely occur beyond the acute stages.[27]

The outcome of CVST is therefore generally favourable and aggressive and potentially dangerous therapeutic intervention should be confined to those patients who deteriorate rapidly despite heparin or who demonstrate poor prognostic indicators.

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