Cerebral venous thrombosis: an update

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Cerebral venous thrombosis (CVT) is a rare type of cerebrovascular disease that can occur at any age, including in neonates, and it accounts for 0·5% of all stroke. The widespread use of neuroimaging now allows for early diagnosis and has completely modified our knowledge on this disorder. CVT is more common than previously thought and it is recognised as a non-septic disorder with a wide spectrum of clinical presentations, numerous causes, and usually a favourable outcome with a low mortality rate. MRI with T1, T2, fluid-attenuated inversion recovery, and T2* sequences combined with magnetic resonance angiography are the best diagnostic methods. D-dimer concentrations are raised in most patients but normal D-dimers do not rule out CVT, particularly in patients who present with isolated headache. Heparin is the first-line treatment, but in a few cases more aggressive treatments, such as local intravenous thrombolysis, mechanical thrombectomy, and decompressive hemicraniectomy, may be required.

Introduction

Cerebral venous thrombosis (CVT)—ie, thrombosis of the intracranial veins and sinuses—is a rare type of cerebrovascular disease that affects about 5 people per million and accounts for 0·5 % of all stroke. CVT was first recognised at the beginning of the 19th century[1] and it was long thought to be an infective disorder that commonly affected the superior sagittal sinus and resulted in bilateral or alternating focal deficits, seizures, and coma, which usually led to death. At this time, CVT was commonly diagnosed at autopsy and usually showed haemorrhagic lesions, which, by analogy with arterial stroke, was thought to contraindicate the use of heparin.[2,3] In the past 25 years, the widespread use of neuroimaging has aided early diagnosis of CVT and has thus completely modified the current information we have on this disorder. CVT is now typically recognised as a non-septic disorder with various clinical presentations and a usually favourable outcome, with mortality well below 10%. MRI and magnetic resonance angiography are the best diagnostic methods for diagnosis and heparin is the first-line treatment.[4–8] However, the diagnosis of CVT is still commonly overlooked or delayed because of the remarkable diversity of its clinical symptoms, modes of onset, and neuroimaging signs; furthermore, a cause cannot be found in about 15% of cases, the individual outcome may still be difficult to predict, and the disorder may occasionally worsen despite anticoagulation. CVT thus remains a diagnostic and therapeutic challenge. In recent years, some progress has been made either from individual studies that focused on specific clinical, MRI, genetic, or therapeutic aspects or from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)—a multicentre prospective cohort of 624 adult patients.[9]

Aetiology

Several disorders can cause, or predispose patients to, CVT (figure 1). These disorders include all medical, surgical, and gyneco-obstetric causes of deep vein thrombosis in the legs, genetic and acquired prothrombotic disorders, cancer, haematological diseases, vasculitis and other inflammatory systemic disorders, pregnancy and puerperium, infections, as well as several local causes—such as brain tumours, arteriovenous malformations, head trauma, CNS infections, and infections of the ear, sinus, mouth, face, or neck.[2,8,9] Diagnostic and therapeutic procedures such as surgery, lumbar puncture, jugular catheter, and some drugs—in particular oral contraceptives, hormonal replacement therapy, steroids, and oncology treatments—can also cause or predispose people to CVT. However, the relative weight of these cases varies in different countries.[10]

CVT is typically multifactorial, which means that the identification of a risk factor or even of a cause should not deter clinicians from looking for other risk factors, particularly congenital thrombophilia. In ISCVT,[9] 44% of the patients had more than one cause or predisposing factor, and congenital or genetic thrombophilia was present in 22% of patients.[9] Besides the classic

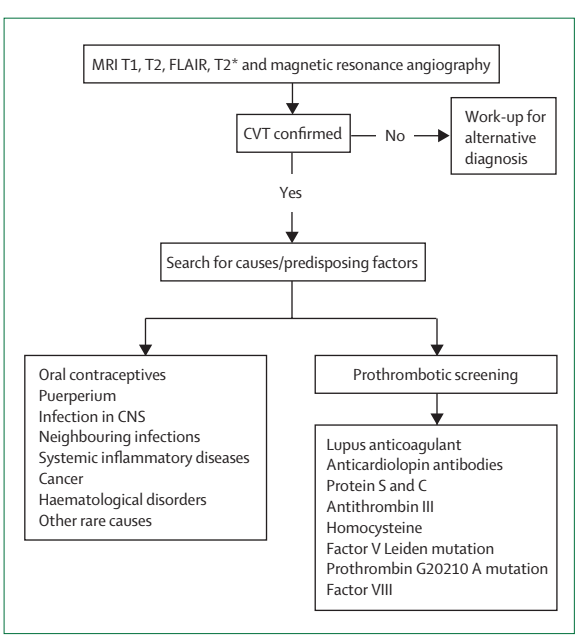

Figure 1: **A flow chart for the diagnosis of CVT**

deficiencies in antithrombin III, protein C, and protein S and having the factor V Leiden or prothrombin gene mutations,[6,11] recent studies have emphasised the role of hyperhomocysteinaemia[12–14] and have addressed new gene polymorphisms of the coagulation and fibrinolytic system.

Hyperhomocysteinaemia, a disorder that is defined as having increased plasma homocysteine concentrations, is an independent and strong risk factor for CVT and is present in 27–43% of patients and 8–10% of controls, with an odds ratio from four[12,13] to nearly seven.[14] Results are more conflicting for post-methionine load increment of homocysteine, which was strongly associated with CVT in one study[12] but not associated in another.[13] No significant independent association has been identified between the C677T mutation in the methylene tetrahydrofalate reductase gene (*MTHFR*) and CVT.[12,13] Whether low serum folate concentrations, which are associated with hyperhomocysteinaemia, are an independent risk factor[13] is still unknown.[12] It is likely that low folate concentrations play a part, particularly during pregnancy and in those with deficient nutritional status and low socioeconomic conditions. Whether or not the correction of hyperhomocysteinaemia, with folic acid alone or in combination with cobalamin and pyridoxine, will help to reduce the risk of CVT in these patients remains to be tested.

Among newly identified gene polymorphisms in the coagulation and fibrinolytic systems, no independent association was found between the protein C promoter CG haplotype and CVT. However, this polymorphism did increase the risk in patients who carried the factor II G20210A mutation, with an odds ratio rising from 14·7 (95% CI: 2·83–75·3) with the factor II mutation alone, to 19·8 (95% CI: 2·1–186·5) with the combination of both mutations.[15] For classic congenital thrombophilia and hyperhomocysteinaemia,[12] the risk is increased when the protein C promoter CG haplotype is associated with oestrogen treatment (odds ratio 24 [2·26–127·3]).[15] In a study with 77 patients, there was no significant association between CVT with polymorphisms of the thrombin activable fibrinolysis inhibitor or of the protein Z genes.[16] Other studies are ongoing and it is very likely that new genetic risk factors for venous thrombosis in the coagulation and fibrinolysis systems will be found in patients with deep vein thrombosis and in those with CVT and hyperhomocysteinaemia. Testing for congenital thrombophilia should thus be systematic in CVT, even when there is a known cause because: firstly, the presence of congenital thrombophilia potentiates the risk of venous thrombosis associated with other disorders and, secondly, because it is important to look for the disorder in family members so that preventive measures in high-risk situations can be taken.[6,11]

Various recent anecdotal case reports have found other causes to add to the already very long list of causes of CVT: spontaneous intracranial hypotension,[17] thalidomide used in a patient with multiple myeloma,[18] Cushing's syndrome,[19] tamoxifen,[20–22] erythropoietin used as a treatment[23] and a doping drug in sport,[24] high altitude as reported in the Himalayas,[25] phyto-estrogens,[26] and Shiatsu massage (an oriental technique of neck massage).[27] Owing to the continuous finding of new causes, the proportion of cases of unknown causes is lower in recent series (around 15%).[6,9] The search for a cause in CVT requires an extensive initial work-up and, when no cause is found, a long follow-up with repeated investigations. In some patients initially interpreted as idiopathic, a general disease can be discovered some months later.[5]

Clinical aspects

CVT presents with a remarkably wide spectrum of signs and modes of onset, thus mimicking numerous other disorders. The most common symptoms and signs are headache, seizures, focal neurological deficits, altered consciousness, and papilloedema, which can present in isolation or in association with other symptoms. According to the grouping of symptoms and signs, four main patterns have been identified: isolated intracranial hypertension, focal syndrome, cavernous sinus syndrome, and subacute encephalopathy; however, there are many other presentations (panel 1).[5,8,11]

Clinical presentation of CVT is affected by age of patient, time between onset and admission to hospital, location of CVT, and the presence of parenchymal lesions. Patients with chronic course or delayed clinical presentation may show papilloedema on fundoscopy, but this finding is less common in acute cases.[28] Isolated thrombosis of the different sinuses and veins results in diverse clinical pictures. In cavernous sinus thrombosis, ocular signs dominate the clinical picture with orbital pain, chemosis, proptosis, and oculomotor palsies. Isolated cortical vein occlusion produces motor or sensory deficits and seizures. In occlusion of the sagittal

***Panel 1:* Presenting symptoms of CVT**

Common symptoms
Isolated intracranial hypertension
Focal syndrome (deficit and/or seizure)
Diffuse encephalopathy
Any combination of the above

Rare symptoms
Cavernous sinus syndrome
Subarachnoid haemorrhage
Thunderclap headache
Attacks of migraine with aura
Isolated headache
Transient ischaemic attacks
Tinnitus
Isolated psychiatric symptoms
Isolated or multiple cranial nerve palsies

sinus motor deficits, bilateral deficits and seizures are typical, whereas presentation as an isolated intracranial hypertension syndrome is not common. Patients with isolated thrombosis of the lateral sinus present mostly as isolated intracranial hypertension. However, if the left transverse sinus is occluded aphasia usually follows. When the deep cerebral venous system is occluded, the clinical picture is usually more severe with coma, mental troubles, and motor deficits, which are usually bilateral. More limited thrombosis of the deep venous system can cause relatively mild symptoms.[29] In patients with parenchymal lesions, the clinical picture is more severe. Patients are more likely to be comatose or to have motor deficits, aphasia, and seizures and are less likely to present with isolated headache. Focal or generalised seizures, including status epilepticus, are more common than in other stroke types. Seizures are more typical in patients with parenchymal lesions, sagittal sinus and cortical vein thrombosis, and motor or sensory defects.[30]

Many other unusual presentations have been described: isolated headache, sometimes of the thunderclap type, transient ischaemic attacks, attacks of migraine with aura, isolated psychiatric disturbances, tinnitus, isolated or multiple cranial nerve involvement, and subarachnoid haemorrhage.[5–8,11]

The possibility of isolated headache as the only symptom of CVT has recently been emphasised. The diagnosis of CVT is particularly difficult in such patients, particularly if the results from computed tomography and cerebrospinal fluid are normal. This was reported in 17 patients among 123 consecutive patients recruited from both a stroke unit and an emergency headache centre.[31] Headache was present in the absence of intracranial hypertension, subarachnoid haemorrhage, or meningitis. Such cases are essentially associated with lateral sinus thrombosis, which should not be mistaken for lateral sinus hypoplasia. The exact mechanism of the headache remains unknown: stretching of nerve fibres in the walls of the occluded sinus is a possibility as well as it being a local inflammatory reaction as suggested by the frequent contrast enhancement of the sinus wall surrounding the clot—known as the "empty delta sign". Because all patients were treated in this series, it is impossible to know whether CVT would have recovered spontaneously or whether the thrombotic process would have extended with occurrence of new symptoms. However, because headache is by far the most common initial symptom, it is important to recognise CVT in patients with isolated headache in order to start treatment as early as possible.

Diagnosis

Neuroimaging of the thrombosed vessel

The diagnosis of CVT is based on neuroimaging but, in contrast to arterial strokes, brain imaging by itself is of little positive value because it usually shows non-specific lesions, such as haemorrhages, infarcts, or oedema in isolation or in combination, and it can be normal in up to 25% of patients. The key to the diagnosis is the imaging of the venous system itself, which may show the occluded vessel or the intravascular thrombus. The current gold standard is the combination of MRI to visualise the thrombosed vessel and magnetic resonance venography to detect the non-visualisation of the same vessel.[6,7,11] MRI alone is limited by flow artifacts that can lead to false positives and the absence of hyperintense signal on T1 and T2-weighted images at the onset of acute thrombosis. During the first 3–5 days the thrombosed sinus is isointense on T1 and hypointense on T2, and thus very difficult to differentiate from normal veins. The diagnostic yield of magnetic resonance venography alone is limited by the fact that, as with all other angiographic techniques, it does not differentiate between thrombosis and hypoplasia, a typical diagnostic dilemma for lateral sinuses.[6,7,11] Even with the combination of MRI and magnetic resonance venography, the diagnosis can still be difficult, particularly in isolated cortical vein thrombosis, which, in the absence of the characteristic cord sign on non-contrast computed tomography scan or on MRI,[32,33] occasionally requires conventional angiography.[34] In fact, the interobserver agreement for the diagnosis of the location of CVT is not perfect, especially in the case of cortical vein thrombosis.[35]

Some studies have highlighted the value of echoplanar susceptibility-weighted images (T2*), which, in contrast to T1 and T2, show the thrombosis as a hypointense signal associated with the magnetic susceptibility effect, similar to that reported for intracerebral haemorrhages.[36–38] In a series of 39 patients, a hypointense signal using T2* was detected in 90% of sites of venous thrombosis at the first MRI investigation, whereas a hyperintense signal was detected on T1 in 84% of sites.[38] The better sensitivity of T2* was clearly significant within the first 3 days of symptom onset, with respective frequencies of hyposignal on T2* in over 90% and of hypersignal on T1 in about 70%. Similarly, thrombosed cortical veins, even in the absence of visible occlusion on magnetic resonance venography, were more typically detected with T2* (97%) than with T1 (78%) or fluid-attenuated inversion recovery (FLAIR; <40%). Thus T2* seems to be of additional value for the diagnosis of CVT. T2* is particularly useful in isolated cortical venous thrombosis and during the very early days of acute CVT when T1 and T2 lack sensitivity[38] (figure 2). The diagnostic yield of the combination of MRI (T1, T2, FLAIR, T2*) and magnetic resonance venography is such that conventional angiography is nowadays very rarely required.

By contrast, the presence of a hyperintense signal of the thrombosed sinus on diffusion-weighted images

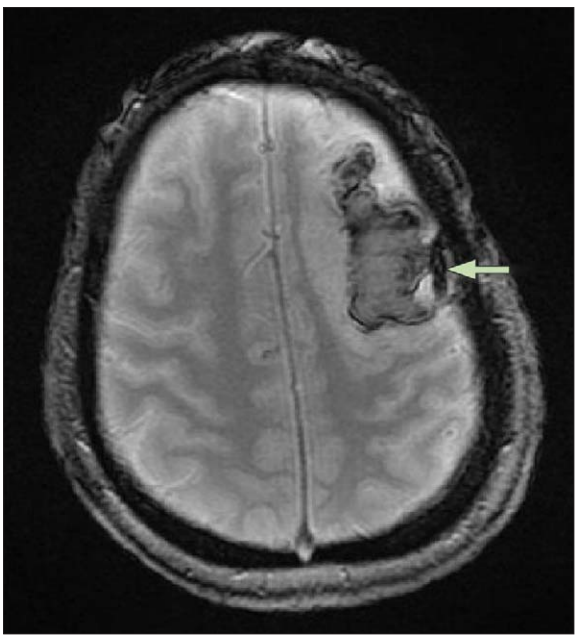

Figure 2: **Axial T2* susceptibilty-weighted image**
A typical magnetic susceptibility effect is detected (green arrow) with a tubular aspect suggestive of a thrombosed cortical vein, which is responsible for an intracerebral haematoma.

has a low diagnostic sensitivity since it is detected in only 10–40% of cases.[39–41] It may, however, be useful to predict non-recanalisation but the clinical relevance of this finding remains to be assessed.[41]

Neuroimaging of parenchymal abnomarlities with diffusion-weighted MRI

The consequences of venous thrombosis on the brain parenchyma are highly variable, with T1 and T2-weighted images showing no abnormality in up to 30% of cases and, in other patients, a localised or diffuse brain swelling with normal or abnormal signal suggestive of oedema, infarction, or haemorrhage. Changes in diffusion-weighted images were first noted in single case reports[42,43] and later in a small series of fewer than 20 patients.[44–49] The inclusion criteria in these studies were variable: some included only patients with non-haemorrhagic brain lesions on T2-weighted imaging,[45,46,49] whereas other studies also included patients with a normal MRI[47] or with haemorrhagic lesions.[39,47] Given the wide spectrum of parenchymal changes and the diversity of inclusion criteria, it is not surprising that various patterns have been reported on diffusion-weighted images, not only between patients but also within patients, and that in the absence of very large series, the exact frequency of these various patterns remains unknown. Except for one study which showed in most patients a decreased apparent diffusion coefficient, which is suggestive of cytotoxic oedema,[48] the most common pattern is a heterogeneous signal intensity with normal or increased apparent diffusion coefficient corresponding to vasogenic oedema.[39,45–47,49] A third less common pattern is that of decreased diffusion with complete resolution and no lesion on follow-up T2-weighted imaging,[45,49] which has been reported mostly in patients with seizures.[49] The overall diffusion-weighted imaging and apparent diffusion coefficient pattern is very different from that of arterial infarcts, and is mostly suggestive of vasogenic oedema and far less commonly of cytotoxic oedema. This difference shows that so-called venous infarcts have little in common with arterial infarcts and probably explains, at least partly, the much better recovery reported in those with CVT.

D-dimer measurement

Because of the wide variety and non-specificity of the presenting symptoms of CVT, it would be of great practical interest to have a test that would be easy to do in emergency care and would confidently rule out CVT. Several studies[50–54] have tested the value of D-dimer measurements because in deep venous thrombosis of the legs, low values (<500 ng/mL) have a high negative predictive value. Indeed, in most patients with recent CVT, D-dimer concentrations are increased, so a negative D-dimer assay may make the diagnosis of CVT very unlikely.[51–53] This holds true in patients who present with encephalic signs in whom D-dimers are normal in only 4% of cases but not in those who present with isolated headache. In a series of 73 patients with CVT of less than 30 days' duration, 26% of those who presented with isolated headache had normal D-dimer concentrations.[54] Thus, a negative D-dimer assay cannot rule out CVT in the setting of a recent isolated headache.[50,54]

Prognosis

A meta-analysis of several recent prospective series, in particular the large ISCVT cohort,[9,55–60] confidently established the vital and functional prognosis of patients with acute CVT, showing a 15% overall death or dependency rate. Long-term predictors of poor prognosis are CNS infection, any type of cancer, deep venous system thrombosis, intracranial haemorrhage, Glasgow Coma Scale score on admission of greater than nine, mental status disorder, being older than age 37 years, or being a man. This predictive model, derived form the ISCVT cohort,[9] was validated in an independent cohort.[61]

In the acute phase of CVT, the case-fatality is around 4%. Predictors of mortality at 30 days are depressed consciousness, mental status disorder, thrombosis of the deep venous system, right hemispheric haemorrhage, and posterior fossa lesions. The main cause of acute death is transtentorial herniation, secondary to a large haemorrhagic lesion, multiple

***Panel 2:* Summary of CVT treatment following European Federation of Neurological Societies guidelines[65]**

Antithrombotic treatment

Acute phase

No contraindication for anticoagulation:

- Body-weighted subcutaneous low-molecular-weight heparin in full therapeutic dosage or APPT (two times above normal values) dose-adjusted intravenous heparin

Worsening despite best medical treatment, other causes of deterioration excluded:

- Local intravenous thrombolysis*, or mechanical thrombectomy*

Prevention of recurrent thrombotic events with oral anticoagulants

CVT related to a transient risk factor, 3–6months

Idiopathic CVT or related to mild hereditary thrombophilia, 6–12 months

Recurrent CVT or severe hereditary thrombophilia, indefinite

Symptomatic treatment

Antiepileptics

Acute phase

- Patients with acute seizures
- Patients with focal parenchymal lesions*
- Patients with focal neurological deficits*

Prevention of seizures after the acute phase

- Patients with acute seizures
- Patients with focal haemorrhagic lesions*

Treatment of intracranial hypertension

Threatened vision

- Lumbar puncture (if no parenchymal lesions)
- Acetazolamide
- Surgical procedures (lumboperitoneal shunt, ventriculoperitoneal shunt, optic nerve fenestration)

Impairment of consciousness or herniation

- Osmotic therapy
- Sedation and hyperventilation
- Hemicraniectomy*

*indicates debated or optional.

lesions, or diffuse brain oedema.[62] Other causes of acute death include status epilepticus, medical complications, and pulmonary embolism.[63] Deterioration after admission occurs in about 23% of patients, with worsening of mental status, headache, or focal deficits, or with new symptoms such as seizures. A new parenchymal lesion is present in one-third of patients who deteriorate.[64] Fatalities after the acute phase are predominantly associated with the underlying disorder.[64]

The individual prognosis is difficult to predict, but the overall vital and functional prognosis of CVT is far better than that of arterial stroke, with about two-thirds of patients recovering without sequelae.

Treatment

Acute treatment

Recent guidelines[65] have been published for the treatment of CVT, which combines causal treatment to specifically manage the various causes, antithrombotic treatment, and symptomatic treatment—ie, treatment of intracranial hypertension, seizures, headache, and visual failure (panel 2).

The aims of antithrombotic treatment in CVT are to recanalise the occluded sinus or vein, to prevent the propagation of the thrombus, and to treat the underlying prothrombotic state—in order to prevent venous thrombosis in other parts of the body, such as pulmonary embolism—and to prevent the recurrence of CVT.[5,8,11,65] Anticoagulants with body-weight-adjusted subcutaneous low-molecular-weight heparin or dose-adjusted intravenous heparin are widely used as first-line therapy on the basis of three randomised trials, a meta-analysis,[8] and numerous large open series such as the ISCVT in whom over 80% of the 624 patients were anticoagulated.[9]

Despite numerous case reports and small series, systematic reviews[66,67] of thrombolysis in CVT, show no good evidence to support the use of either systemic or local thrombolysis in this disorder. There is a potential publication bias in the current published work, with possible under-reporting of cases with poor outcome and complications. Treatment and assessment were non-blind, leading to bias in assessing outcomes. In ISCVT, 13 patients were treated with local thrombolysis. Five (38·5%) were dead or dependent 6 months after CVT. These results are worse than those in other studies, but may indicate the prevailing results in clinical practice. However, if patients deteriorate despite adequate anticoagulation and other causes of deterioration have been ruled out, thrombolysis or thrombectomy may be considered in selective centres with expertise in interventional radiology.[6,8,11]

In patients with isolated intracranial hypertension, if papilloedema threatens vision, a lumbar puncture to remove cerebrospinal fluid is required before starting heparin. This is usually followed by a rapid improvement in headache and visual function.

If intracranial pressure is severely raised, general recommendations should be followed, including raising the head off the bed, treatment with glycerol or mannitol and admission to an intensive care unit with sedation, hyperventilation, and intracranial pressure monitoring.[65] There is no indication for steroids having a benefit, even in patients with parenchymal lesions.[68] In patients with impending herniation due to unilateral hemispheric lesion, decompressive hemicraniectomy can be life-saving[69,70] and even allow a good functional recovery.

Patients who present with seizures should receive antiepileptic drugs because they are at risk of recurrence.[30] By contrast, the risk of occurrence of seizures in patients without seizures on admission is

very low, except for patients with parenchymal lesions on admission.[30]

Management after the acute phase

The aim of continuing anticoagulation after the acute phase is to prevent recurrent CVT and other venous thrombosis, including pulmonary embolism. Recurrent CVT is very rare and also difficult to document, particularly if a previous follow-up magnetic resonance angiography is not available. Other thrombotic events, in particular deep venous thrombosis in the limbs or pelvis and pulmonary embolism, occur in up to 5% of patients.[9] Following the evidence and recommendations in systemic deep venous thrombosis, anticoagulation with warfarin for 6–12 months is recommended in survivors of acute CVT, aiming at an international normalised ratio of two or three. More prolonged oral anticoagulation is reserved for patients with inherited or acquired prothrombotic disorders, including patients with antiphospholipid antibody syndrome.

Seizures occur in 11% of the patients, more so if the patient had seizures in the acute phase or had a haemorrhagic parenchymal lesion.[30,71] Such patients can be placed on antiepileptic drugs to prevent seizure recurrence. However, the optimum duration of antiepileptic drug treatment is unknown.

Severe visual loss is fortunately a very rare event nowadays.[9,72,73] If visual acuity decreases during follow-up and is not explained by ocular causes, increased intracranial pressure must be rapidly ruled out and managed accordingly. Fenestration of the optic nerve sheet has also been used to relieve pressure and prevent optic nerve atrophy.

Despite the general good recovery after CVT, about 50% of survivors may feel depressed or anxious[74] and minor cognitive or language deficits may prevent them from resuming their previous level of professional activity.[75] Patients should be reassured of the very low risk of recurrence of CVT and encouraged to return to previous occupations and hobbies.

As pregnancy and puerperium are risk factors for CVT, an important question to consider is the risk of future pregnancies in women who have had a history of CVT. Six studies have addressed this issue,[9,56,76–78] with a total of 855 women under observation, of whom 83 became pregnant after their CVT (101 pregnancies). In these studies, the risk of complications during future pregnancies was low: 88% of the pregnancies ended in a normal birth, the remaining being prematurely terminated by voluntary or by spontaneous abortion. There were no instances of recurrent CVT and there were only two cases of deep venous thrombosis. Therefore, on the basis of available evidence, CVT and even pregnancy-related or puerperium-related CVT are not a contraindication for future pregnancies. Antithrombotic prophylaxis during pregnancy is probably unnecessary, unless a prothrombotic disorder or a previous thromboembolism was identified. Women should be advised not to become pregnant while on coumadin, because of its teratogenic effects.

CVT in neonates

CVT in children has long been recognised[3] but it is only recently that large neuroimaging-based series have been reported.[79–88] The disorder affects all age groups with an estimated incidence of 0·67 per 100 000 per year and a preponderance in neonates.[79] In older children, CVT shares many similarities with adult CVT except for a slight male preponderance, and an increased chance of infective cause and worse functional prognosis.[80,81] However, in neonates the causes, clinical presentation, outcome, and management are very different.

Maternal gestational risk factors seem to play a part, particularly pre-eclampsia or hypertension being present in 26% and 10% respectively of women in two large series,[82,83] and diabetes (gestational or chronic) also present in 26% and 10% in the same series.[83] However, in a large series of 69 neonates, gestational diabetes was present in only 3% of women.[79] About 75% of neonates have an acute illness at the time of diagnosis, mostly dehydration, cardiac defects, sepsis, or meningitis.[79,82,85] There is a male predominance in some series[84] but not in others.[82] The most common presenting symptoms are seizures, which occur in about two-thirds of cases, and respiratory distress or apnoea, present in one-third of cases.[79,82] Other symptoms include poor feeding, weight loss, acidosis, hypotonia, and lethargy. As in adults, the superior sagittal sinus and lateral sinuses are the most typically involved but the straight sinus and the deep venous system are more commonly (about one-third of cases) involved than in adults.[82] An infarct is present on neuroimaging in 40–60% of cases,[79,82] with a very common haemorrhagic component and an intraventricular haemorrhage in 20% of cases.[82]

Data about outcome are somewhat conflicting. In the most recent series, there was one death out of 42 cases but 79% of children were left with some degree of impairment: 59% with cognitive impairment, 67% with motor impairment, and 41% with seizures, which is higher than in previous reports.[80,86,87]

Treatment is mostly symptomatic:[79,82,85] rehydration, antibiotics for suspected sepsis, antiepileptic drugs, and cardiac surgery for some cardiac malformations. There is no consensus as regards to the use of heparin, which was tested in a pilot study[88] without apparent detrimental effect but is far less extensively used in adults—less than 10% in the most recent series.

In summary, although MRI also allows an early diagnosis in neonates, the non-specific presentation of neonatal CVT and its common association with an acute illness make the diagnosis difficult. The functional outcome is more severe than in adults and heparin is far less used. Further work is needed to develop

Search strategy and selection criteria

References were selected from an electronic Medline search from 1995 to April 2006 using key words from "cerebral vein thrombosis", "cerebral veins" and "dural sinus and thrombosis". References in English, French, Portuguese and Spanish were included. Many references for this review came from the authors' files.

standardised guidelines for the assessment and treatment of neonatal CVT.

CVT in elderly patients

CVT in elderly people has received little attention. In ISCVT, 8·2% of the patients were age 65 years or older.[89] They differed in some respects from CVT in younger patients: there was less frequent isolated intracranial hypertension, more frequent depressed consciousness and mental status changes, and carcinoma was more frequent as a cause. Prognosis was worse with 49% of patients dead or dependent at the end of follow-up. CVT should thus be added to the long list of disorders that cause depressed consciousness or mental changes in elderly patients and an extensive search for cancer should be pursued. Because of an increased risk of further thrombotic events, anticoagulation for more than 6 months may be warranted.[89]

The near future of clinical research in CVT

There are still many unsolved issues in the pathophysiology, diagnosis, and management of CVT. Because of the small number of cases diagnosed each year, even at reference centres, cooperation between a network of interested centres is essential. The participation of hospitals from developing countries is particularly welcome to enable a global picture of CVT. The identification of new gene polymorphisms in the coagulation and fibrinolytic system, their role in CVT, and their interaction with exogenous risk factors will continue. Efforts to develop a simple screening laboratory test to detect CVT in patients who present with isolated headache are also a priority. New magnetic resonance sequences can be developed to increase the accuracy of diagnosis of CVT. Finally, the level of evidence supporting our current management decision, local thrombolysis, decompressive hemicranioectomy, antiepileptic prophylaxis, and duration of anticoagulation treatment should be increased through prospective registries, case–control studies and, when feasible, randomised controlled trials.

Contributors

MGB wrote the first draft, which was reviewed and significantly modified after extensive discussion with JF. Both read and approved the final version of the manuscript.

Conflicts of interest

MGB and JF have been and still are investigators and/or members of various committees in several trials of stroke treatment and prevention, but none on CVT.

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