Cerebral Venous Thrombosis: a practical guide

Leonardo Ulivi[1], Martina Squitieri[2*], Hannah Cohen[3,4], Peter Cowley[5], David J Werring[6,7]*

[1] Department of Experimental and Clinical Medicine, Neurological Clinic, Pisa University, Pisa, Italy.

[2] NEUROFARBA Department, University of Florence, Florence Italy.

[3]Haemostasis Research Unit, Department of Haematology, University College London, London, UK.

[4]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK.

[5]Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, UK.

[6]Stroke Research Centre
UCL Queen Square Institute of Neurology
First Floor
Russell Square House
10-12 Russell Square
London WC1B 5EH

[7]Comprehensive Stroke Service, University College London Hospitals NHS Foundation Trust, London, UK.

**authors contributed equally*

Total word count: 3930 (excluding abstract references, figure legends and tables)

Abstract

All neurologists need to be able to recognise and treat cerebral venous thrombosis. It is difficult to diagnose, partly due to its relative rarity, its multiple and various clinical manifestations (different from "conventional" stroke, and often mimicking other acute neurological conditions), and because it is often challenging to obtain and interpret optimal and timely brain imaging. Although cerebral venous thrombosis can result in death or permanent disability, it generally has a favourable prognosis if diagnosed and treated early. Neurologists involved in stroke care therefore also need to be aware of the treatments for cerebral venous thrombosis (with varying degrees of supporting evidence): the mainstay is prompt anticoagulation but patients who deteriorate despite treatment can be considered for endovascular procedures (endovascular thrombolysis or thrombectomy) or neurosurgery (decompressive craniotomy or shunt insertion). This review summarises current knowledge on the risk factors, diagnosis, treatment and prognosis of cerebral venous thrombosis in adults, and highlights some areas for future research.

Introduction

Definition and pathophysiology

Cerebral venous thrombosis (CVT) is an important cause of stroke in young adults (mean age 33 years with a two-thirds female preponderance) (1) caused by complete or partial occlusion of the cerebral major cerebral venous sinuses (cerebral venous sinus thrombosis; CVST) or the smaller feeding cortical veins (cortical vein thrombosis). CVT is frequently missed or diagnosed late because it can mimick other acute neurological conditions and can only be recognised with optimal and timely brain imaging (2). CVT was found in 9.3% of one consecutive autopsy series,(3) suggesting that it might often be missed in life. CVT generally has a favourable prognosis if diagnosed and treated early.(4) The mainstay of acute treatment is anticoagulation with parenteral heparin, but patients who deteriorate despite treatment can be considered for endovascular procedures (endovascular thrombolysis or thrombectomy) or neurosurgery (decompressive craniotomy or shunt insertion).(5, 6)

CVT accounts for 0.5%–1.0% of unselected stroke admissions(7) and is about three times as common in women than men,(8, 9) probably partly due to its association with pregnancy, the puerperium and the use of oestrogen-containing oral contraceptives.(10)

Blood from the brain drains through small cerebral veins into larger veins of the deep venous system (including the internal cerebral veins, basal veins and vein of Galen), which then empty into dural sinuses (including the straight sinus, transverse sinuses and sagittal sinus); these in turn drain mainly into the internal jugular veins (**Figure 1**). Changes in blood stasis, vessel wall abnormalities, and the composition of the blood (Virchow's triad) lead to an imbalance between prothrombotic and fibrinolytic processes, predisposing to progressive venous thrombosis. Obstruction of venous vessels induces increased venous pressure, reduced capillary perfusion and locally increased cerebral blood volume. Although initially compensated for by the dilatation of cerebral veins and the recruitment of collateral vessels, continued elevation of venous pressure can cause vasogenic oedema (due to blood–brain barrier disruption) and decreased cerebral perfusion pressure and cerebral blood flow with tissue infarction;(11) thus, both cytotoxic and vasogenic oedema can occur.(12) The venous territories are less well defined than are arterial territories due to extensive anastomoses between cortical veins, which allow the development of alternative venous drainage pathways after an occlusion. CVT can also block CSF absorption through the arachnoid villi, which then leads to raised intracranial pressure (with or without tissue injury), typically in association with superior sagittal sinus obstruction.

These pathophysiological changes can cause the typical focal neurological symptoms and signs of CVT, which depend on the territory of the brain that has impaired venous drainage, the acuity of the occlusion (sudden or gradual), the degree of collateralisation, and the degree of associated tissue injury (see "Clinical presentation" and **Table 1**). The slow growth of the thrombus and collateralisation of venous vessels probably accounts for the often gradual onset of symptoms, frequently over days, weeks or months.

This review aims to provide general neurologists, stroke physicians, general physicians, emergency physicians and neurosurgeons with advice on diagnosis and treatment of patients with CVT. Our management suggestions are in part based on guidelines from American Heart Association and American Stroke Association (AHA/ASA)(13) and the more recent European Stroke Organization and European Academy of Neurology (ESO-EAN) Guidelines(14). However, where data are limited, we have offered suggestions based on expert opinion or clinical experience.

Search strategy and selection criteria

We searched PubMed, Medline and Cochrane Library, from 1995 to May 2020 using the search (((sinus*[TI] AND thrombosis[TI]) OR (thrombosis[TI] AND cerebral [TI] AND (venous[TI] OR vein*[TI] OR sinus*[TI])) OR ("Sinus Thrombosis, Intracranial"[MESH]) OR (intracranial[TI] AND thrombosis[TI]))) and other relevant terms including: "aetiology", "pathogenesis", "risk factors", "diagnosis", "therapy", "treatment", "therapeutics", "management", "anticoagulant", "endovascular", "decompressive craniectomy", "prognosis". We limited the search to human studies and those published in English. This search was supplemented by reviewing additional references from included studies.

Risk factors

Important risk factors for CVT (most likely first) are oestrogen-containing oral contraceptives, prothrombotic (hypercoagulable) conditions (genetic or acquired), pregnancy and the puerperium, infections, malignancy,(15) head injury (causing direct trauma to venous structures) and inflammatory diseases (7) (**Table 2**). The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)(8) found that up to 85% of adult patients have at least one risk factor; the most common was use of oral contraceptives, followed by a prothrombotic condition (more often genetic than acquired).

Heritable thrombophilias associated with CVT include factor V Leiden and the G20210A prothrombin gene mutation(16), as well as antithrombin, protein C and S deficiency.(17) Homozygosity for the C655T *MTHFR* polymorphism has also been reported; this is present in approximately 10% of the normal population and is usually not associated with thrombosis, although it may predispose to hyperhomocysteinaemia, which in turn can lead to thrombosis(17)). In order to understand better the genetic factors involved in CVT, a large consortium genome-wide association study (18) is ongoing.

The most common acquired prothrombotic states are pregnancy, the puerperium and oral contraceptives,(19) which explain the threefold increase in risk of CVT among women of childbearing potential.(10) Moreover, obesity seems to increase the risk of CVT, especially in females using oral contraceptives(20). Antiphospholipid antibody syndrome is also an important (and treatable) cause of CVT that should be sought in all unexplained cases.(21) In

patients aged over 55 years, CVT is equally prevalent between the sexes;(22) malignancy is a frequent cause (in 25% of patients).

Other less common causes of CVT include local infection (ears, sinuses, mouth, face, or neck), head injury with trauma to the venous sinuses, iron deficiency anaemia, inflammatory diseases (systemic lupus erythematosus, Behçet's disease, granulomatosis with polyangiitis, inflammatory bowel disease and sarcoidosis), haematological disorders (myeloproliferative diseases associated with *JAK2* V617F mutations, paroxysmal nocturnal haemoglobinuria, and haemoglobinopathies).(23)

Many patients have multiple risk factors, so unless a very clear cause is found (e.g. direct invasion of a sinus by a local ear infection) then most patients need a thorough search for all risk factors (particularly thrombophilias).

Clinical presentation

The symptoms of CVT range from minor to life-threatening(11) depending on the sinuses and veins involved, the extent of brain parenchymal injury, chronicity, and the effect on intracranial pressure (**Table 1**). It is helpful to classify the manifestations of CVT into clinical syndromes, which depend on the predominant site of venous occlusion, though often these overlap.(10) The superior sagittal sinus is most frequently affected (in 62%), causing a wide range of potential presentations with combinations of headache (from raised intracranial pressure), focal neurological deficits (e.g. hemisensory loss, hemiparesis, hemianopia, from parenchymal injury) and seizures (**Figure 2**). Transverse sinus thrombosis (in about 45%, see **Figure 3**) typically causes temporo-parietal haemorrhagic infarction (from occlusion of the vein of Labbé) with headache and, if left sided, aphasia, sometimes with seizures. Sigmoid sinus involvement is rare in isolation but can cause mastoid pain and, very rarely, lower cranial neuropathies. Thrombosis of the deep veins (internal cerebral veins, vein of Galen, straight sinus) is present in about 18% and often causes oedema of the thalami, which is challenging to diagnose because it causes mental status alteration, coma and gaze palsy (**Figure 4**). Isolated intracranial hypertension (from sagittal sinus thrombosis, often longstanding) usually leads to headache, papilloedema and visual impairment. Finally, cavernous sinus thrombosis is much rarer but easy to recognise due to its characteristic presentation with eye pain, chemosis, proptosis and oculomotor palsy.(7)

Headache is the commonest symptom, reported in about 90% of cases; indeed, it is the only manifestation in about 25% of patients.(11) Unfortunately, CVT-related headache does not have specific diagnostic features, though is usually progressive in onset (hours or days); much less often, thunderclap headache can be the first symptom, presumably related to subarachnoid bleeding.(24) Headache from CVT can be localised or diffuse, sometimes with migrainous headache or aura features.(24-26) We suggest that neuroimaging should be performed in presence of red flags for CVT, which include a headache that is: new-onset and persistent; worse with the Valsalva manoeuvre; not improved with regular analgesia; or in a person with typical risk factors or papilloedema (**Table 3**).(27)

Stroke-like focal neurological symptoms occur in up to 40% of patients,(8, 19)] though are often not as sudden in onset as arterial ischaemic stroke or intracranial haemorrhage; motor symptoms are most frequent, followed by visual impairment and aphasia (especially if the left transverse sinus is involved), whereas sensory symptoms are less common.(19) In a large multicentre cohort, there was brain infarction in 36.4% of patients, haemorrhagic transformation in 17.3%, and intraparenchymal haemorrhage in 3.8%.(19) In a patient with a stroke syndrome, factors that point towards CVT rather than arterial ischaemic stroke include headache and seizures,(28)(reported in up to 40% cases)(8) and infarction on neuroimaging that does not fit a single arterial territory and usually has a prominent haemorrhagic component (see below; **Figure 3**). Reduced consciousness, ranging from drowsiness to coma, can result from raised intracranial pressure, deep venous infarction (**Figure 4**), or both.(29)

The clinical presentation of CVT varies with age. Most affected children are aged younger than 6 months; in neonates nonspecific symptoms of lethargy, bulging fontanel, or seizures can occur (30, 31). Compared with younger patients, those older than 65 years less commonly develop intracranial hypertension, while mental status and alertness disturbances are common; the prognosis of CVT (for dependency, death and recurrent thrombotic events) is worse in elderly patients(22).

Diagnosis

Patients with suspected CVT require urgent neuroimaging to confirm the diagnosis, using either CT or MR to visualise the thrombus directly, show impaired venous flow, or both (**Table 4**).(32) No laboratory test can rule out CVT. The D-dimer level can be normal, especially in mild or chronic cases,(33, 34) but it has a high negative predictive value for excluding CVT in the specific situation of patients with isolated headache,(33) and therefore has been suggested as a component of a pre-imaging probability score, along with a normal neurological examination and CT scan of head , to avoid unnecessary neuroimaging.(35) Routine blood studies (erythrocyte sedimentation rate, blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time) should ideally be done before starting anticoagulation treatment (although where there is clinical urgency anticoagulation is started before receiving these results, relying on initial clinical evaluation for evidence of a bleeding diathesis or renal or liver disease).(32)

Neuroimaging

Non-contrast CT scan of head is a useful first test (and the first brain imaging in suspected stroke in many hospitals): in about one-third of patients it shows specific signs including venous sinus or deep vein hyperdensity,(36) (**Figure 3**) sometimes termed the dense triangle sign (high attenuation in the sagittal sinus or deep cerebral veins in a triangle shape)(37) or the cord sign (high attenuation due to thrombus in the transverse sinus).(38) CT can also detect ischaemia (typically not respecting arterial boundaries, often with some haemorrhagic transformation), parenchymal or subarachnoid haemorrhages or signs of oedema (**Figure 2**). However, plain CT is normal in up to 30% of patients and, even if abnormal, is not specific.(7, 39) Thus all patients with suspected CVT require further imaging beyond a plain CT scan.

The European Stroke Organization Guidelines suggest MR venography or CT venography for confirming the diagnosis(32). We prefer CT venography as a “lumen-based” rather than “flow-based” method: compared to the gold standard of digital subtraction angiography, it has very good diagnostic accuracy (sensitivity of 95% and specificity of 91%).(40) CT venography can show absent flow in thrombosed veins or sinuses and partial circumferential enhancement of thrombosed venous sinuses (e.g. the empty delta sign;(41) **Figure 5**). However, false positives can be due to normal sinus hypoplasia or arachnoid

granulations.(42) MR venography, performed with time-of-flight sequences, also allows assessment of the absence of flow in thrombosed sinuses (**Figure 1A**), without the need for contrast medium (43) but with a higher risk of false positives (for example in the frequent case of a non-dominant (hypoplastic) transverse sinus).

MR imaging is the most sensitive technique for demonstrating the presence of the thrombus, using sequences sensitive to the magnetic susceptibility effects of paramagnetic iron-containing blood components (T2*-weighted gradient echo or susceptibility-weighted imaging; SWI) (**Figure 1D**); the appearance of the clot on different MR imaging sequences varies depending on its age(44) so can also help to date CVT onset. MR imaging is also the best technique to assess parenchymal involvement fully (ischaemia, haemorrhages, oedema, swelling); furthermore, poorer recanalisation rate in DWI-hyperintense thrombosed sinuses can occur.(45)

Catheter intra-arterial digital subtraction angiography (DSA) should be used to confirm the diagnosis only when CTV or MR venography are inconclusive.(11, 32) The relationship between dural arteriovenous fistulae and CVT is complex and not fully understood. A dural arteriovenous fistula can rarely complicate CVT, a phenomenon presumed due to opening of arteriovenous pathways in the wall of the sinus during occlusion or recanalisation. It is important to detect the fistula early (requiring intra-arterial DSA) to allow treatment, e.g. with embolisation. Conversely, CVT can occur during development of an arteriovenous fistula. Whatever the relationship, clinicians need to be aware that these pathologies can co-exist and that they require specific treatments. Isolated cortical vein thrombosis is often visible on susceptibility-weighted sequences but can be challenging diagnose, and sometimes requires intra-arterial DSA to confirm.

Treatment

Treatment should be started as soon as the diagnosis of CVT is clearly confirmed, with anticoagulant therapy, treating any underlying cause when detected (e.g. dehydration, sepsis, stopping any prothrombotic medications), control of seizures, and management of intracranial hypertension. **Figure 6** provides a suggested treatment decision flow chart.

Anticoagulation

The evidence supporting anticoagulation in CVT is fairly weak, being based on data from four randomised controlled trials with methodological limitations. The first placebo-controlled trial of intravenous heparin for CVT (given on average rather late, at about 4 weeks), undertaken in Berlin, was stopped early after an interim analysis showed increased mortality in the placebo arm.(46) Another trial (at multiple centres in The Netherlands and UK) in 60 participants randomly allocated to nadroparin (a low molecular weight heparin (LMWH)) or placebo (but excluding those requiring lumbar puncture for raised intracranial pressure) found a non-significant improvement in the proportion of participants achieving a good functional outcome for LMWH.(47) A Cochrane review of these two trials (n=79) (48) found that unfractionated heparin or LMWH treatment was associated with a non-significant reduction in death or dependency (relative risk 0.46; 95% CI, 0.16–1.31). Only three patients developed a new intracranial haemorrhage, all allocated to placebo. Major extracranial bleeding occurred in one patient randomised to LMWH. Two other trials from India (n=97) used only non-contrast CT for diagnosis and were published only as abstracts (so could not be included in the meta-analysis) but also suggested benefit from heparin.

LMWH is the preferred anticoagulant treatment for CVT, also based on limited trial evidence. An open-label randomised controlled trial including 66 patients with CVT concluded that LMWH in full anticoagulant doses is more effective than unfractionated heparin (49) with a lower risk of major bleeding or death. Although there are no large high-quality randomised trials,(50) LMWH is recommended in guidelines from the European Stroke Organisation(32) and is our standard practice; we usually give this as split-dose (i.e. two divided doses per 24 hours) to minimise the risk of haemorrhagic complications. The European Stroke Organisation guideline advises that unfractionated heparin should be used in patients with renal insufficiency or in patients requiring very rapid reversal of anticoagulation (e.g. imminent neurosurgical intervention).(32) However, the summary of product characteristics for LMWH do not include severe renal impairment among contraindications. We therefore use reduced dose LMWH in severe renal impairment, with specialist haematological advice about dosing and anti-Xa level monitoring. Although their alarming radiological appearance can cause anxiety, haemorrhagic venous infarction, intracranial

haemorrhage, or isolated subarachnoid haemorrhage are NOT contraindications for anticoagulant treatment in CVT.(51)

Thrombosis of the smaller cerebral cortical veins is usually in association with CVT, though isolated cortical vein thrombosis can rarely occur. The most sensitive neuroimaging technique to diagnose this is using blood-sensitive MRI sequences (T2*-weighted gradient echo or SWI). A review of 116 cases of isolated cortical vein thrombosis suggested that, as expected, raised intracranial pressure was less common than in CVT where major sinuses are involved. Most patients (80%) were treated with anticoagulation, with good outcome (6% in-hospital mortality); this approach seems to be reasonable in the absence of controlled trial data.(52)

Preventing further venous thrombotic events

Initial anticoagulation with LMWH (as soon as the diagnosis is confirmed) is followed by a longer-term anticoagulation to prevent further venous thrombotic events; the risk of recurrent CVT is about 2–7% per year, and the risk of other venous thrombosis is about 5% per year.(8) Current guidelines recommend using oral vitamin-K antagonist (usually warfarin in the UK) at standard-intensity (target internationalised normalised ratio [INR] 2.5, range 2.0–3.0) for between 3 and 12 months.(32) The optimal duration of anticoagulation in CVT is uncertain because of the lack of randomised trials or prospective studies and in practice is decided based on the underlying risk factors for recurrence and bleeding.(11, 53) However, the following suggested scheme (see **Figure 6**) is supported by expert opinion and guidelines:(11) patients with one episode of CVT and transient risk factors (dehydration, drugs (e.g. oral contraceptives), infections, trauma, surgical interventions), should receive anticoagulation for 3 to 6 months; patients with one episode of CVT of unknown cause should continue anticoagulation for 6 to 12 months; those patients with two or more CVTs (or one episode and a severe prothrombotic condition with a high ongoing thrombotic risk) are usually recommended to have lifelong anticoagulation. A study comparing efficacy and safety of short-term (3–6 months) versus long-term (12 months) anticoagulation after CVT (EXtending oral antiCOAgulation treatment after acute Cerebral Vein Thrombosis- EXCOA-CVT) is ongoing.(54)

The direct oral anticoagulants (DOACs) are an effective, safe and convenient alternative to vitamin-K antagonists and have changed the management of atrial fibrillation and venous

thromboembolism. Moreover, DOACs do not require INR monitoring or dose adjustments, have fewer interactions with other medications or need for dietary restrictions, and a lower rate of intracranial bleeding compared with vitamin-K antagonists.(55) However, current guidelines do not recommend DOACs in patients with CVT because of the limited quality of the available evidence. A recent exploratory randomised, open-label clinical trial randomly allocated 120 participants with CVT to dabigatran versus warfarin for 6 months (Re-SPECT CVT)(56). There were no recurrent venous thromboembolic events in either treatment group, while major bleeding occurred in one patient allocated to dabigatran and two treated with warfarin. The authors concluded that both dose-adjusted warfarin and dabigatran are safe and effective in secondary prevention of any venous thrombo-embolic events after CVT. Further randomised controlled studies of DOACS for CVT are underway (e.g. Study of Rivaroxaban for CeREbral Venous Thrombosis (SECRET); NCT03178864). Currently we do not use DOACs routinely after CVT but consider them in patients considered to have a high risk of intracranial bleeding with warfarin. However, depending on the results of ongoing trials, including longer-term follow up, DOACs might become the standard of care for CVT in future.

Endovascular treatment

While anticoagulation aims to prevent the progression of the clot and alter the balance of thrombosis and lysis, endovascular treatment aims to reduce thrombus burden rapidly either by locally administrating fibrinolytic agents or mechanically removing the thrombus.(57, 58) Small non-randomised studies, case series and case reports describe a recanalisation rate of 70–90%, but with a substantial rate of intracranial haemorrhage of about 10%.(58, 59) The Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial, a randomised blinded-ended trial designed to establish the efficacy of endovascular treatment, was prematurely stopped for futility(60, 61): at one-year follow-up, 22 intervention patients (67%) had an mRS score of 0 to 1 compared with 23 control patients (68%) (relative risk ratio, 0.99; 95% CI, 0.71–1.38). There were no statistically significant differences in mortality or symptomatic intracranial haemorrhage. We therefore only rarely consider endovascular treatment in severe cases of CVT that do not improve or deteriorate despite anticoagulant therapy; it is probably most effective for acute rather than well-established thrombosis. We recommend full multidisciplinary discussion (neurology, neuroradiology, sometimes neurosurgery) for complex cases before considering endovascular treatment.

European Stroke Organization guidelines (which incorporate the factors we consider in clinical discussions) recommend that endovascular treatment should only be considered in patients with a high pre-treatment risk of poor outcome(32, 62) (**Table 5**).

Treatment of elevated intracranial pressure

In the acute phase, elevated intracranial pressure (due to space-occupying brain oedema, infarction, intracranial haemorrhage) and brain herniation can rapidly lead to severe brain injury and death. Patients judged to have, or to be at high risk of, raised intracranial pressure should ideally be managed on a neurological critical care unit with rapid access to endovascular and neurosurgical teams. Medical therapy for elevated intracranial pressure includes osmotic therapy (such as mannitol), hyperventilation (PCO_2 30–35 mmHg) and elevating the head of the bed. Therapeutic lumbar puncture has been proposed to reduce intracranial pressure in patients with isolated intracranial hypertension,(63) but data in acute CVT are inconclusive. Lumbar puncture is safe in patients without lesions on CT scan of head but is contraindicated in patients with large lesions with risk of herniation (64). Similarly, there is no available evidence in favour of carbonic anhydrase inhibitors, such as acetazolamide, although they can be useful in patients with severe headaches or threat to vision. Corticosteroids should not be used except in the presence of underlying inflammatory diseases (e.g. Behçet's disease, systemic lupus erythematosus).

In presence of brain herniation or midline shift ("malignant CVT"), medical therapy alone is often not sufficient to control raised intracranial pressure. Decompressive craniectomy allows the swelling brain to expand and could favour collateral vein drainage in CVT by reducing intracranial pressure. No randomised study has been done, so evidence is limited to single-centre small cohort studies, case series and case reports. Observational data suggest that decompressive surgery can be life-saving; it has a favourable outcome in more than 50% of patients, with a mortality rate of 15–18%.(5, 65) Despite the low quality of available evidence, the ESO-EAN strongly recommend decompressive hemicraniectomy in otherwise well patients with parenchymal lesion(s) and impending herniation(14). Neuroradiological features that should lead to consideration of craniectomy include: uncal herniation; midline shift (> 5 mm); and herniation induced ischaemia in the territory of the posterior cerebral artery territory (which is vulnerable to local mass effect and raised intracranial pressure).(5) A persistent intracranial pressure > 20 cmH_2O is also suggested as a criterion for surgery. The

optimal timing of anticoagulation after hemicraniectomy is not clear, being reported between 24 hours to 8 days.(5, 66) The bone flap is often replaced after 3–6 months, when the brain swelling resolves(5). Given the high probability of poor functional outcome in survivors of hemicraniectomy after CVT, a full and frank discussion with the patient (or, more likely, family members or carers) is essential before intervention. Ventricular shunting does not appear to prevent death or herniation, so is not recommended to treat raised ICP in CVT.(6)

Seizures

There is limited evidence regarding primary or secondary prevention of seizures in CVT. In those with both a symptomatic seizure and parenchymal injury from infarction or haemorrhage, antiepileptic drug treatment is approriate. It is less clear whether to treat patients with a seizure but no supratentorial brain lesion, or with a lesion but no clinical seizures; the guidelines are inconsistent. When seizures are treated, it is important to avoid antiepileptic drugs that interact with the planned anticoagulant treatment. There is no evidence about the optimal duration of treatment. We base our practice on current data that suggest that in seizures associated with oedema, infarction, or haemorrhage, treatment should be continued for at least 1 year.(51)

Prognosis

CVT generally has a favourable outcome, with a complete functional recovery reported in about 75% of patients; however about 15% die or become dependent.(8) In the acute setting, risk factors for a poor outcome include: male sex, older age, confusion or coma, intracranial haemorrhage, deep vein involvement, infection and malignancy.(8) Despite good physical recovery, many survivors have symptoms of depression or anxiety, or cannot return to work because of cognitive impairment(67). Cognitive decline is under-investigated and under-recognised, especially when deep veins are involved, where it is reported in up to one-third of patients(68). The recurrence risk after CVT is low: 2–7% for CVT and 4–7% for systemic thromboembolism;(8) patients with a severe thrombophilic disorder and those stopping anticoagulant therapy early being at highest risk.(11)

Key points

- CVT is a rare but important cause of stroke in young adults; diagnosis is challenging because of the many and varied symptoms, and depends on rapid and appropriate neuroimaging
- Once CVT is diagnosed a careful search for an underlying cause (e.g. oral contraceptive use or thrombophilia) is essential
- Treatment includes anticoagulation with parenteral heparin, prevention of recurrent seizures, and decompressive neurosurgery in patients with large space-occupying venous infarction, haemorrhage or both); endovascular therapy remains unproven
- Anticoagulation is generally recommended for 3-12 months; direct oral anticoagulants are a promising alternative to warfarin, but further trial data are needed

Competing interests

DJW has received honoraria from Bayer, Portola, and Alnylam, outside the submitted work.

Authorship statement

LU and MS prepared the first draft with DJW. HC, PC and DJW reviewed the manuscript for intellectual content. DJW and PC prepared the figures. JB, RB, MH, AC and DW wrote the manuscript and are responsible for its content.

Funding

DJW receives research funding support from the British Heart Foundation and the Stroke Association. This work was undertaken at University College London Hospitals NHS Foundation Trust/University College London, who received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Provenance and peer review. Commissioned. Externally peer reviewed by José Ferro, Lisbon, Portugal, and Teddy Wu, Christchurch, New Zealand.

Figure legends

Fig 1: Time-of-flight MR venogram of the normal major cerebral veins and venous sinuses. (image courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 51158).

Fig 2: Sagittal sinus thrombosis. (A) MR venogram showing absent venous flow signal in the middle third of the superior sagittal sinus (white arrows); (B) Axial gadolinium-enhanced T1-weighted MR image showing an irregular filling defect of the superior sagittal sinus (white arrow); (C) Sagittal gadolinium-enhanced T1-weighted MR image also showing a focal filling defect inicating thrombus (white arrow); (D) Axial susceptibility-weighted imaging (SWI) showing low signal indicating blood products (thrombus) in the superior sagittal sinus (white arrow).

Fig 3: Transverse venous sinus thrombosis. (A) Area of haemorrhagic infarction of the right temporoparietal region not respecting arterial boundaries with swelling and oedema (white arrows); (B) CT venogram showing absent contrast filling of the right transverse sinus (white arrow); (C) severe haemorrhagic infarction with worsening mass effect that was treated with hemicraniectomy (white arrows).

Fig 4: Deep cerebral venous thrombosis. (A) Axial T2-weighted image showing bilateral thalamic high signal (white arrows) in a 21-year old woman (taking the oral contraceptive pill) who presented with headache, drowsiness and confusion; (B) SWI in the same patient showing petechial haeomorrhage within the areas of thalamic infarction (white arrows), and low signal in the deep cerebral and internal veins consistent with thrombosis (white dashed arrow); (C) unenhanced CT scan of head showing hyperdense acute thrombus in the straight sinus and vein of Galen (white arrow); (D) SWI showing low signal in the internal cerebral veins consistent with venous thrombosis (black arrow); (E) Axial diffusion-weighted MR scan showing restricted diffusion in the right thalamus (indicating venous ischaemia; white arrow) in an 18-year-old woman who presented with headache and drowsiness, and who was taking the oral contraceptive pill; (F) MR venogram showing loss of flow signal in the deep venous system (straight sinus, vein of Galen, and internal and basal veins; approximate expected position shown by the dashed small white arrows).

Figure 5: The "empty delta" sign. Axial contrast-enhanced CT scan, where the contrast outlines a filling defect of the sagittal sinus (due to thrombis), creating the shape of the greek letter delta (Δ) (image courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 57576).

Table 1. Clinical manifestations of cerebral venous thrombosis according to occlusion site

Occluded sinus/vein	Clinical presentation
Transverse sinus (44–73%)	If isolated without infarction: asymptomatic or headache If left transverse sinus with venous infarction: aphasia If extending into the contiguous sinuses: intracranial hypertension, consciousness disturbance, focal cerebral signs and cranial nerve palsies (IX-X-XI) If extending into the cerebellar vein: headache, vomiting and limb or gait ataxia.
Superior sagittal sinus (39–62%)	Isolated intracranial hypertension: • headache • blurred vision • visual loss • nausea, vomiting • cranial nerve palsy (differential diagnosis of pseudotumor cerebri) Focal brain lesion due to venous infarction: • aphasia • hemianopia • hypoesthesia and hemiparesis • seizures Isolated psychiatric symptoms (rare)
Sigmoid sinus (40–47%)	Pain in the mastoid region Combinations of VI-VII-VIII cranial nerve palsies
Deep venous system (10.9%)	Mental status disturbances – reduced arousal Diffuse encephalopathy or coma Motor deficits (bilateral or fluctuating alternating paresis)
Cortical veins (3.7–17.1%)	Focal neurological signs according to location Seizures
Cavernous sinus (1.3–1.7%)	Headache, ocular pain, chemosis, proptosis, ocular nerve palsy (III, IV, VI and the ophthalmic division of V) Fever (when there is an infective cause)

Table 2. Risk factors for cerebral venous thrombosis (from reference (8))

Gender-specific risk factors	
Oral contraceptives	54.3%
Puerperium	13.8%
Pregnancy	6.3%
Hormonal replacement therapy	4.3%
Systemic conditions	
Iron deficiency anaemia	9.2%
Malignancy	7.4%
Myeloproliferative diseases	2.9%
Dehydration	1.9%
Inflammatory bowel disease	1.6%
Systemic lupus erythematosus	1%
Behçet's disease	1%
Thyroid disease	1.7%
Neurosarcoidosis	0.2%
Obesity	-
Genetic/acquired thrombophilia	
Antiphospholipid antibody syndrome	5.9%
MTHFR gene mutation/hyperhomocysteinaemia	4.5%
Factor V Leiden mutation	-
Prothrombin gene mutation	-
Protein S/C deficiency	-
Antithrombin deficiency	-
Nephrotic syndrome	0.6%
Polycythaemia/thrombocythaemia	-

Infections	
Ears, sinuses, mouth, face, neck	8.2%
Other	4.3%
Central nervous system	2.1%
Mechanical factors	
Surgery/Neurosurgery	2.7%/ 0.6%
Lumbar puncture	1.9%
Head trauma	1.1%
Drugs	
Cytotoxic	0.8%
Lithium	n.d.
Vitamin A	n.d.
IV immunoglobulin	n.d
Ecstasy	n.d
Vascular abnormalities	
Dural arteriovenous fistulae	1.6%
Arteriovenous malformations	0.2%
Other venous abnormalities	0.2%

Table 3. When to suspect CVT

Presence of CVT risk factors (e.g. oral contraceptive, malignancy, anaemia)
New headache or head pain with different features in patients with previous primary headache
Symptoms or signs of raised intracranial pressure (e.g. papilloedema)
Focal neurological signs
Altered consciousness
Seizures

Table 4. Neuroradiological features of CVT

	CT + CT venogram	MR + MR venogram
Typical Findings	Sinus or vein hyperdensity	1 week: isointense in T1 and hypointense in T2W images
	Dense triangle sign	2 weeks: hyperintense in T1 and T2W images
	Empty delta sign	> 2 week: variable in T1 and T2, hypointense in GRE and SWI
	Cord sign	DWI hyperintensity
	Absence of flow in thrombosed sinuses	Venous wall enhancement
		Absence of flow in thrombosed sinuses
Advantages	Easily available	No radiation exposure
	Fast	No contrast medium required
	Reduced motion artefact	Good visualisation of parenchyma
		Detection of cortical and deep vein thrombosis
Disadvantages	Ionising radiation	Time consuming
	Use of contrast medium	Motion artefact
	Poor detection of small parenchymal abnormalities	Reduced availability
	Low sensitivity in small cortical and deep thrombosis	Contraindicated in some patients (e.g. cardiac devices)

Table 5. Prognostic score for CVT (69)

Prognostic Variable	Risk points
Malignancy	2
Coma	2
Deep venous thrombosis	2
Mental status disturbances	1
Male sex	1
Intracranial haemorrhage	1

< 3: low risk of poor outcome

≥ 3: high risk of poor outcome[55].

The score is available as a free app.

(NB we have not been able to find it on the Apple App store)

References

1. Coutinho JM, Zuurbier SM, Stam J. Declining mortality in cerebral venous thrombosis: a systematic review. Stroke. 2014;45(5):1338-41.
2. Linn J, Ertl-Wagner B, Seelos KC, Strupp M, Reiser M, Bruckmann H, et al. Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. AJNR Am J Neuroradiol. 2007;28(5):946-52.
3. Towbin A. The syndrome of latent cerebral venous thrombosis: its frequency and relation to age and congestive heart failure. Stroke. 1973;4(3):419-30.
4. Canhao P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F, et al. Causes and predictors of death in cerebral venous thrombosis. Stroke. 2005;36(8):1720-5.
5. Avanali R, Gopalakrishnan MS, Devi BI, Bhat DI, Shukla DP, Shanbhag NC. Role of Decompressive Craniectomy in the Management of Cerebral Venous Sinus Thrombosis. Front Neurol. 2019;10:511.
6. Lobo S, Ferro JM, Barinagarrementeria F, Bousser MG, Canhao P, Stam J, et al. Shunting in acute cerebral venous thrombosis: a systematic review. Cerebrovasc Dis. 2014;37(1):38-42.
7. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162-70.
8. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F, Investigators I. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664-70.
9. Coutinho JM, Ferro JM, Canhao P, Barinagarrementeria F, Cantu C, Bousser MG, et al. Cerebral venous and sinus thrombosis in women. Stroke. 2009;40(7):2356-61.
10. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791-8.
11. Saposnik G, Barinagarrementeria F, Brown RD, Jr., Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
12. Rother J, Waggie K, van Bruggen N, de Crespigny AJ, Moseley ME. Experimental cerebral venous thrombosis: evaluation using magnetic resonance imaging. J Cereb Blood Flow Metab. 1996;16(6):1353-61.
13. Saposnik G, Barinagarrementeria F, Brown RD, Jr., Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
14. Ferro JM, Bousser MG, Canhao P, Coutinho JM, Crassard I, Dentali F, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203-13.
15. Gulati D, Strbian D, Sundararajan S. Cerebral venous thrombosis: diagnosis and management. Stroke. 2014;45(2):e16-8.
16. Biousse V, Conard J, Brouzes C, Horellou MH, Ameri A, Bousser MG. Frequency of the 20210 G-->A mutation in the 3'-untranslated region of the prothrombin gene in 35 cases of cerebral venous thrombosis. Stroke. 1998;29(7):1398-400.
17. Marjot T, Yadav S, Hasan N, Bentley P, Sharma P. Genes associated with adult cerebral venous thrombosis. Stroke. 2011;42(4):913-8.

18. Cotlarciuc I, Marjot T, Khan MS, Hiltunen S, Haapaniemi E, Metso TM, et al. Towards the genetic basis of cerebral venous thrombosis-the BEAST Consortium: a study protocol. BMJ Open. 2016;6(11):e012351.
19. Duman T, Uluduz D, Midi I, Bektas H, Kablan Y, Goksel BK, et al. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. J Stroke Cerebrovasc Dis. 2017;26(8):1848-57.
20. Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, et al. Risk of Cerebral Venous Thrombosis in Obese Women. JAMA Neurol. 2016;73(5):579-84.
21. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-40.
22. Ferro JM, Canhao P, Bousser MG, Stam J, Barinagarrementeria F, Investigators I. Cerebral vein and dural sinus thrombosis in elderly patients. Stroke. 2005;36(9):1927-32.
23. Passamonti SM, Biguzzi E, Cazzola M, Franchi F, Gianniello F, Bucciarelli P, et al. The JAK2 V617F mutation in patients with cerebral venous thrombosis. J Thromb Haemost. 2012;10(6):998-1003.
24. de Bruijn SF, Stam J, Kappelle LJ. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet. 1996;348(9042):1623-5.
25. Newman DS, Levine SR, Curtis VL, Welch KM. Migraine-like visual phenomena associated with cerebral venous thrombosis. Headache. 1989;29(2):82-5.
26. Agostoni E. Headache in cerebral venous thrombosis. Neurol Sci. 2004;25 Suppl 3:S206-10.
27. Do TP, Remmers A, Schytz HW, Schankin C, Nelson SE, Obermann M, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92(3):134-44.
28. Kalita J, Chandra S, Misra UK. Significance of seizure in cerebral venous sinus thrombosis. Seizure. 2012;21(8):639-42.
29. Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. J Thromb Haemost. 2018;16(10):1918-31.
30. Wasay M, Dai AI, Ansari M, Shaikh Z, Roach ES. Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States. J Child Neurol. 2008;23(1):26-31.
31. Shevell MI, Silver K, O'Gorman AM, Watters GV, Montes JL. Neonatal dural sinus thrombosis. Pediatr Neurol. 1989;5(3):161-5.
32. Ferro JM, Bousser MG, Canhao P, Coutinho JM, Crassard I, Dentali F, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203-13.
33. Alons IM, Jellema K, Wermer MJ, Algra A. D-dimer for the exclusion of cerebral venous thrombosis: a meta-analysis of low risk patients with isolated headache. BMC Neurol. 2015;15:118.
34. Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2012;10(4):582-9.
35. Smith E, Kumar V. BET 1: Does a normal D-dimer rule out cerebral venous sinus thrombosis (CVST)? Emerg Med J. 2018;35(6):396-7.

36. Garetier M, Rousset J, Pearson E, Tissot V, Gentric JC, Nowak E, et al. Value of spontaneous hyperdensity of cerebral venous thrombosis on helical CT. Acta Radiol. 2014;55(10):1245-52.
37. Sonoo T, Gunshin M, Son D, Nakajima S, Kitamura K, Yahagi N, et al. Cerebral venous thrombosis and "Dense Triangle Sign" on unenhanced head computed tomographic scan. Am J Emerg Med. 2014;32(2):192 e3-4.
38. Vijay RK. The cord sign. Radiology. 2006;240(1):299-300.
39. Chiras J, Bousser MG, Meder JF, Koussa A, Bories J. CT in cerebral thrombophlebitis. Neuroradiology. 1985;27(2):145-54.
40. Wetzel SG, Kirsch E, Stock KW, Kolbe M, Kaim A, Radue EW. Cerebral veins: comparative study of CT venography with intraarterial digital subtraction angiography. AJNR Am J Neuroradiol. 1999;20(2):249-55.
41. Lee EJ. The empty delta sign. Radiology. 2002;224(3):788-9.
42. Dior U, Shelef I, Joshua B, Gluck O, Puterman M. Arachnoid granulation masquerading as lateral sinus vein thrombosis. Isr Med Assoc J. 2012;14(3):198-9.
43. Bonneville F. Imaging of cerebral venous thrombosis. Diagn Interv Imaging. 2014;95(12):1145-50.
44. Isensee C, Reul J, Thron A. Magnetic resonance imaging of thrombosed dural sinuses. Stroke. 1994;25(1):29-34.
45. Favrole P, Guichard JP, Crassard I, Bousser MG, Chabriat H. Diffusion-weighted imaging of intravascular clots in cerebral venous thrombosis. Stroke. 2004;35(1):99-103.
46. Einhaupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, et al. Heparin treatment in sinus venous thrombosis. Lancet. 1991;338(8767):597-600.
47. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke. 1999;30(3):484-8.
48. Stam J, De Bruijn SF, DeVeber G. Anticoagulation for cerebral sinus thrombosis. Cochrane Database Syst Rev. 2002(4):CD002005.
49. Misra UK, Kalita J, Chandra S, Kumar B, Bansal V. Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: a randomized controlled trial. Eur J Neurol. 2012;19(7):1030-6.
50. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev. 2017;2:CD001100.
51. Coutinho JM, Stam J. How to treat cerebral venous and sinus thrombosis. J Thromb Haemost. 2010;8(5):877-83.
52. Coutinho JM, Gerritsma JJ, Zuurbier SM, Stam J. Isolated cortical vein thrombosis: systematic review of case reports and case series. Stroke. 2014;45(6):1836-8.
53. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation. 2010;121(25):2740-6.
54. Miranda B, Aaron S, Arauz A, Barinagarrementeria F, Borhani-Haghighi A, Carvalho M, et al. The benefit of EXtending oral antiCOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke. 2018;13(7):771-4.
55. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018;154(5):1121-201.
56. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al. Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis: A Randomized Clinical Trial. JAMA Neurol. 2019.

57. Rahman M, Velat GJ, Hoh BL, Mocco J. Direct thrombolysis for cerebral venous sinus thrombosis. Neurosurg Focus. 2009;27(5):E7.
58. Siddiqui FM, Dandapat S, Banerjee C, Zuurbier SM, Johnson M, Stam J, et al. Mechanical thrombectomy in cerebral venous thrombosis: systematic review of 185 cases. Stroke. 2015;46(5):1263-8.
59. Ilyas A, Chen CJ, Raper DM, Ding D, Buell T, Mastorakos P, et al. Endovascular mechanical thrombectomy for cerebral venous sinus thrombosis: a systematic review. J Neurointerv Surg. 2017;9(11):1086-92.
60. Coutinho JM, Zuurbier SM, Bousser MG, Ji X, Canhao P, Roos YB, et al. Effect of Endovascular Treatment With Medical Management vs Standard Care on Severe Cerebral Venous Thrombosis: The TO-ACT Randomized Clinical Trial. JAMA Neurol. 2020.
61. Coutinho JM, Ferro JM, Zuurbier SM, Mink MS, Canhao P, Crassard I, et al. Thrombolysis or anticoagulation for cerebral venous thrombosis: rationale and design of the TO-ACT trial. Int J Stroke. 2013;8(2):135-40.
62. Ferro JM, Bacelar-Nicolau H, Rodrigues T, Bacelar-Nicolau L, Canhao P, Crassard I, et al. Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2009;28(1):39-44.
63. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. Neurology. 1999;53(7):1537-42.
64. Canhao P, Abreu LF, Ferro JM, Stam J, Bousser MG, Barinagarrementeria F, et al. Safety of lumbar puncture in patients with cerebral venous thrombosis. Eur J Neurol. 2013;20(7):1075-80.
65. Ferro JM, Crassard I, Coutinho JM, Canhao P, Barinagarrementeria F, Cucchiara B, et al. Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. Stroke. 2011;42(10):2825-31.
66. Pizzi MA, Alejos DA, Siegel JL, Kim BY, Miller DA, Freeman WD. Cerebral Venous Thrombosis Associated with Intracranial Hemorrhage and Timing of Anticoagulation after Hemicraniectomy. J Stroke Cerebrovasc Dis. 2016;25(9):2312-6.
67. de Bruijn SF, Budde M, Teunisse S, de Haan RJ, Stam J. Long-term outcome of cognition and functional health after cerebral venous sinus thrombosis. Neurology. 2000;54(8):1687-9.
68. Bugnicourt JM, Guegan-Massardier E, Roussel M, Martinaud O, Canaple S, Triquenot-Bagan A, et al. Cognitive impairment after cerebral venous thrombosis: a two-center study. J Neurol. 2013;260(5):1324-31.
69. Ferro JM, Bacelar-Nicolau H, Rodrigues T, Bacelar-Nicolau L, Canhao P, Crassard I, et al. Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2009;28(1):39-44.