Cerebral Venous Thrombosis in Adults

James Fleet*, Jonathan Birns and Ajay Bhalla

INTRODUCTION

Cerebral venous thrombosis (CVT) is a heterogeneous condition characterised by thrombotic occlusions of the cerebral veins and dural sinuses. Its risk factors, presentation, and prognosis differ markedly from arterial stroke. The non-specific and variable presentation of CVT means that it can easily be missed or mistaken for other disease processes, and the treating physician requires a high index of suspicion for diagnosis. Neuroimaging options are continually evolving to provide improved accuracy of diagnosis to assist in the initial assessment of this condition. Management has been informed by a steadily increasing evidence base, with endovascular and surgical techniques allowing opportunities to intervene in the natural history of the disease to improve patient outcomes [1-2]. Despite the therapeutic options available, physicians managing this condition need to be aware of potential complications to prevent the poor outcomes that occur in a significant subgroup of patients. The aim of this review is to provide the practising clinician with an overview of the epidemiology, diagnosis and management of a condition that remains a considerable diagnostic and therapeutic challenge in modern clinical medicine.

In March 2013, an electronic database search was performed of MEDLINE, EMBASE, and the Cochrane Library using the following MeSH and keywords: cerebral venous sinus thrombosis; cerebral venous thrombosis; venous sinus thrombosis between the years 1966 and 2013. These search terms were combined with epidemiology; diagnosis; CT; MRI; management; treatment; thrombolysis; surgery; prognosis; randomised trial; meta-analysis. Articles not involving adult patients or not written in English were excluded. Inclusion of articles was based on agreement between two independent reviewers (James Fleet and Ajay Bhalla). The resultant information was supplemented by extensive manual searching of references.

How common is CVT and who is at risk?

Due to a paucity of epidemiological studies, the exact incidence of CVT is unknown. However, studies have shown incidence to vary between 1 to 12 cases per million adults per year with an increased incidence in developing countries [3-5]. Despite its rarity, 10-20% of patients investigated for CVT in emergency settings are later confirmed to have this diagnosis [6]. The largest prospective registry of patients with CVT is the International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVT) cohort [7]. In this group, there was a female predominance with a ratio of 3:1 [8]. It is thought that gender-specific risk factors account for this occurrence, including pregnancy, the puerperium and use of the oral contraceptive pill (OCP), with similar incidences in male and female cohorts in older age groups and prior to the widespread use of the OCP [9]. Indeed, in Dentali et al.’s meta-analytical study, women taking the OCP had an odds ratio (OR) of developing CVT of 5.59 (95%
CI: 3.95 - 7.91) compared with controls [14]. Through similar
mechanisms, CVT is primarily a disease of younger people with
only 8.2% of patients in the ISCVT cohort being over 65 years of age [10].

A multitude of disease states and patient factors have been
implicated in CVT. These risk factors may be conceptualised as
local or systemic with the latter being congenital or acquired
(Table 1). Local causes are predominantly infections of the
central nervous system (CNS) and surrounding structures (often
the ear and paranasal sinuses) [12]. Rates of infectious causes of
CVT are declining in the modern antibiotic era, but account for
a greater proportion of cases in developing countries [13].

A number of congenital thrombophilic states have been
implicated in CVT, and were associated with 22% of patients in
the ISCVT. This contrasts to their role in arterial stroke which has
not been established and is certainly weaker than in CVT [17-
18]. Factor V leiden and prothrombin G20210A gene mutations
are the most common forms of inherited thrombophilia in
Caucasian populations, accounting for 50-60% of cases, and
these mutations have been the most extensively studied in
cases of CVT [19]. In Dentali et al.’s meta-analysis the presence
of Factor V leiden had a pooled OR of 3.38 (95% CI: 2.27 - 5.05)
for developing CVT (similar to that of venous thromboembolism
(VTE) in its entirety) and prothrombin mutations had an OR 9.27
(95% CI: 5.85 - 14.67) (higher than that of VTE in its entirety)
[2,14]. Deficiencies of protein C and protein S have been studied
for a lesser extent; however strong associations have been found
in CVT cases with ORs of 11.1 (95% CI: 1.87 - 66.05) and 12.49
(95% CI: 1.45 - 107.29) respectively [14].

An acquired precipitant often occurs in an individual
presupposed to a hypercoagulable state, multiplying the risk
of developing CVT. For example, Martinelli showed that use
of the OCP by a patient with the prothrombin gene mutation
increased the OR of developing CVT from approximately 10 to
150 compared to controls [11]. Such patients with multiple risk
factors make up 44% of the ISCVT cohort. In most cases, CVT starts in a large venous sinus
thrombosis making up a minority of cases. One or both of the
transverse sinuses are most commonly affected (86%) with the
superior sagittal sinus second most likely to be involved (62%) [7]
(Figure 1). These factors have given rise to three distinct clinical
entities in CVT: intracranial hypertension, focal neurological
deficits and a diffuse encephalopathy. The variable time of onset
of these syndromes, ranging from minutes to weeks, combined
with their evolution and overlap give rise to the considerable
heterogeneity in the symptoms and signs of CVT.

**Table 1: Conditions associated with CVT.**

<table>
<thead>
<tr>
<th>Local</th>
<th>Infectious</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sinusitis, Bacterial Meningitis, Tuberculous Meningitis</td>
<td>Congenital</td>
</tr>
<tr>
<td></td>
<td>Mastoiditis, Malignant otitis externa, Periorbital cellulitis</td>
<td>Haematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acquired</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>Trauma, Lumbar puncture, Neurosurgery, Dural fistulae</td>
<td>Hyperhomocystaeinemia, Polycythaeemia, Thrombocythaemia, Antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haematological malignancy, CNS tumour, Solid organ malignancy outside CNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflammatory bowel disease, Bechet’s disease, Sarcoïdosis, Cerebral vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender-specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy, Puerperium, OCP use, Hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dehydration, Major surgery, Nephrotic syndrome, Spontaneous intracranial hypotension, Drugs e.g. tamoxifen, thalidomide, erythropoietin, Systemic infection e.g. bacteraemia</td>
</tr>
</tbody>
</table>

When occlusion of the cerebral veins occurs, venous hypotension leads to localized disruption of the blood brain barrier with venous haemorrhage and vasogenic oedema as plasma leaks into the interstitial space. Venous hypotension may also lower the cerebral perfusion pressure causing direct cell death and infarction from failure of metabolite delivery, with subsequent cytotoxic oedema. Indeed, perfusion and diffusion weighted MRI have confirmed the presence of both cytotoxic and vasogenic oedema in CVT [25]. Thrombosis in the major cerebral sinuses with elevated venous pressures leads to failure of cerebrospinal fluid (CSF) reabsorption at the arachnoid granulations and the resultant increases in CSF volume leads to a syndrome of intracranial hypertension.

**Clinical features**

In contrast to arterial stroke, the onset of the symptoms
of CVT are frequently sub-acute (with the median time from
symptom onset to admission being 4 days in the ISCVT). The clinical features of CVT are mostly dependent on the anatomical location and extent of the thrombus, although patient age and time from symptom onset to presentation are also important factors [10,12]. In most cases, CVT starts in a large venous sinus and extends to the cortical veins, with isolated cortical vein thrombosis making up a minority of cases. One or both of the transverse sinuses are most commonly affected (86%) with the superior sagittal sinus second most likely to be involved [62%] [7] (Figure 1). These factors have given rise to three distinct clinical entities in CVT: intracranial hypertension, focal neurological deficits and a diffuse encephalopathy. The variable time of onset of these syndromes, ranging from minutes to weeks, combined
with their evolution and overlap give rise to the considerable
heterogeneity in the symptoms and signs of CVT.
The syndrome of isolated intracranial hypertension occurred in 23% of patients in the ISCVT cohort. Typically, it presents with a generalised, severe and dull headache, worsened by valsalva manoeuvre and recumbancy, and papilloedema and subsequent visual impairment may follow. Focal neurological deficits, most commonly mono- or hemiparesis, usually result from haemorrhagic transformation of the venous infarction that develops in approximately half of CVT cases [7,27]. Large cerebral hemispheric venous infarcts or haemorrhages may cause brainstem compression and cerebral herniation. Up to 22% of CVT patients, more so in elderly patients, may present with a diffuse encephalopathy, ranging from confusion and agitation to coma [7,10].

In addition to these 3 clinical syndromes, CVT also commonly presents with headache and/or seizures. Headache is the most common presenting complaint of CVT, present in 90% of cases [4,7]. It may be the only symptom or may complicate any presentation of CVT and occurs without intracranial hypertension in around 15% of patients [26]. The nature of the headache is variable and non-specific, at times mimicking the thunderclap headache of subarachnoid haemorrhage or more commonly presenting insidiously. Headache may be caused by stimulation of meningeal pain fibres due to blood, infection or traction. Nerve fibres in vein walls may also be directly simulated by expanding thrombus [12]. Around 50% of patients are troubled by headaches in the longer term following CVT, and these are most commonly mild and migrainous in nature, although severe headache may occur in up to 14% and should prompt exclusion of re-thrombosis [7,26]. Seizures are more common in CVT than in ischaemic stroke, complicating almost 40% of cases, and the majority are generalised. Predictors of presenting seizure have been found to be supratentorial lesions, cortical vein thrombosis, sagittal sinus thrombosis and puerperal CVT. In contrast, this complication is rare in patients presenting with isolated intracranial hypertension (<3%) [28].

Diagnosis

The comparative rarity and variable presentation make CVT a diagnostic challenge, and delays to diagnosis are common with a mean of 3 days from admission to diagnosis in ISCVT. It should be considered as a differential diagnosis in headache, especially those with thrombotic risk factors and specifically excluded in patient with features of raised intracranial pressure. It is an important differential in younger patients without typical cardiovascular risk factors presenting with focal neurological deficits, particularly if these are sub-acute in onset. The differential diagnosis in patients with disturbance of consciousness is wide but intracranial imaging is usually undertaken in this patient group if no cause is initially apparent.

Imaging for CVT

The diagnosis of CVT is made with neuroimaging, with non-invasive techniques playing the predominant role. Indications of CVT on brain imaging can be divided into direct signs where the thrombus is visualised and indirect signs where accompanying parenchymal changes are seen [29]. In the UK, the speed and accessibility of non-enhanced CT (NECT) scan mean this is often the initial investigation in patients with focal neurology, headache or change in consciousness.

The direct sign of CVT on NECT is the dense vein or cord sign, a homogenous hyperdensity within a thrombosed cortical vein, and can be seen in the first 2 weeks following thrombus formation [30]. If the thrombosis is located in the sagittal sinus, it is known as the filled delta or dense triangle sign; however these features are rare [31]. When contrast is used, CVT can be seen as the empty delta sign, which represents contrast enhancement flowing around a hypodense area in the superior sagittal sinus [32]. After 2 weeks, thrombus is isodense to brain parenchyma and often not seen without contrast enhancement [29]. Parenchymal lesions of haemorrhages and infarcts may be seen on NECT and may cross over arterial boundaries.

Despite the advantages of NECT, false-positives can be due to partial voluming effects caused by bony structures adjacent to sinus and cortical veins. False negatives are also common, with NECT revealing no abnormality in two thirds of patients with CVT [33-34].
Table 2: Summary of imaging modalities in CVT.

<table>
<thead>
<tr>
<th></th>
<th>CT/CTV</th>
<th>MRI/MRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Readily available</td>
<td>Less available, especially in emergency setting</td>
</tr>
<tr>
<td>Cost</td>
<td>Typically cheaper compared to MRI</td>
<td>Often more expensive compared to CT</td>
</tr>
<tr>
<td>Examination time</td>
<td>10 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Other practical considerations</td>
<td>Less patient cooperation required, radiation exposure, possible contrast reactions, inc. nephrotoxicity and allergy</td>
<td>Greater patient cooperation required, higher risk of motion artefact, limitations in patients with pacemakers or claustrophobia</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Relatively easier to interpret images</td>
<td>Expert knowledge required for interpretation</td>
</tr>
<tr>
<td>Direct signs of CVT</td>
<td>Evolving but encouraging evidence base</td>
<td>Traditionally gold standard</td>
</tr>
<tr>
<td>Secondary parenchymal changes</td>
<td>Low resolution</td>
<td>Gold standard, detection of early ischaemic changes</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; CTV, CT venography; MRI, magnetic resonance imaging; MRV, MR venography; CVT, cerebral venous thrombosis.

Table 3: Summary of randomised controlled trials for anticoagulation in CVT.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>N</th>
<th>Intervention</th>
<th>Follow up Duration</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einhäupl, 1991 [49]</td>
<td>Randomised blinded (patient and observer), placebo-controlled single centre trial</td>
<td>20</td>
<td>Heparin infusion for 8 days vs placebo infusion</td>
<td>3 months</td>
<td>0 deaths in treatment group vs 3 (30%) in placebo group, RR 0.14 (95% CI 0.01-2.45)</td>
<td>Trial stopped early after 20 of planned 60 patients enrolled due to a treatment benefit seen</td>
</tr>
<tr>
<td>de Bruijn, 1999 [50]</td>
<td>Randomised double-blind, placebo-controlled multicentre trial</td>
<td>59</td>
<td>3 weeks LMWH (nadroparin) followed by 3 months open label OAC vs 3 weeks of placebo</td>
<td>3 months</td>
<td>4 (12%) death or dependence (OHS of ≥3) in treatment group vs 6 (21%) in placebo group, RR 0.64 (95% CI 0.20-2.05)</td>
<td>49% had ICH on randomisation. No new symptomatic ICH in treatment group</td>
</tr>
<tr>
<td>Misra, 2012 [52]</td>
<td>Randomised open label single centre trial</td>
<td>66</td>
<td>LMWH vs UFH for 14 days followed by OAC</td>
<td>3 months</td>
<td>0 deaths in LMWH group vs 6 deaths (18.8%) in UFH group (p&lt;0.01)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, Low molecular weight heparin; OAC, Oral anticoagulation; UFH, Unfractionated heparin; OHS, Oxford Handicap Scale; ARR, absolute risk reduction; CI, confidence interval; NS, non-significant; CVT, cerebral venous thrombosis; ICH, intracerebral haemorrhage.

Table 4: Rationale and evidence for early medical interventions CVT.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Rationale</th>
<th>Remarks</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>Prevent thrombus propagation, promoting re-canalisation, prevent extra-cerebral VTE</td>
<td>Meta-analysis show trend to reduced death and disability. Although not statistically significant, consistent and clinically meaningful.</td>
<td>Level of Evidence B [49-50]</td>
</tr>
<tr>
<td>Anticoagulation with LMWH over UFH</td>
<td>More predictable anticoagulation, longer duration of action</td>
<td>Lower mortality of LMWH over UFH in one RCT, recommended unless potential need to reverse anticoagulation rapidly</td>
<td>Level of Evidence B [52]</td>
</tr>
<tr>
<td>Endovascular interventions</td>
<td>Application of thrombolytic agents +/- mechanical clot disruption. Potential faster re-canalisation and without systemic anticoagulation</td>
<td>Consider if deterioration despite anticoagulation and no large ICH or cerebral herniation from large infarcts. Unproven efficacy with conflicting results from observational series and case reports. Subject to on-going RCT.</td>
<td>Level of Evidence C [63-64]</td>
</tr>
<tr>
<td>AEDs after seizure</td>
<td>Seizure common in CVT, prevention of deleterious sequelae of seizure</td>
<td>Observation studies show reduced seizure re-occurrence with AEDs in patients presenting with seizure and with parenchymal lesion.</td>
<td>Level of Evidence B [28]</td>
</tr>
<tr>
<td>Prophylactic AEDs</td>
<td>Supratentorial lesion predict seizures, possible prevention</td>
<td>Not recommended. No evidence of efficacy.</td>
<td>Level of Evidence C [2]</td>
</tr>
<tr>
<td>Steroids</td>
<td>May decrease vasogenic oedema</td>
<td>Not recommended. Not effective in case controlled study.</td>
<td>Level of Evidence B [67]</td>
</tr>
<tr>
<td>Decompressive craniectomy for impending cerebral herniation</td>
<td>Reduce ICP</td>
<td>Should be considered for patient with large venous infarcts and haemorrhages causing mass effect with risk of cerebral herniation. Consensus opinion.</td>
<td>Level of Evidence C [69,73]</td>
</tr>
<tr>
<td>LP and acetazolamide in patients with raised ICP at risk of visual loss</td>
<td>Acetazolamide decreases CSF production, LP reduces pressure on optic nerve.</td>
<td>Therapeutic LP and acetazolamide initiation should be undertaken when vision at risk. Consensus opinion.</td>
<td>Level of Evidence C [1]</td>
</tr>
</tbody>
</table>

Level of evidence A: data derived from multiple randomised controlled trials or meta-analysis. Level of evidence B: data derived from a single randomised controlled trial or non-randomised studies. Level of evidence C: consensus opinion of experts, case studies or standards of care.

Abbreviations: LMWH, Low molecular weight heparin; OAC, Oral anticoagulation; UFH, Unfractionated heparin; OHS, Oxford Handicap Scale; ARR, absolute risk reduction; CI, confidence interval; NS, non-significant; CVT, cerebral venous thrombosis; AEDs, anti-epileptic drugs; ICP, intracranial pressure.
Figure 2 Non-enhanced CT showing bilateral hyperdensity within the both the transverse sinuses.

Figure 3 Non-enhanced CT showing dilation and hyperdensity of the straight sinus with a hyperdense superior sagittal sinus (filled delta or dense triangle sign, arrowed).

Figure 4 Non-enhanced CT showing hyperdensity within the vein of Galen and small amount of petechial haemorrhage within a hypodense area of oedema and possible infarction in the left basal ganglia.

Figure 5 T$_1$ gradient echo MRI showing increased susceptibility within the internal cerebral veins and in the left corpus striatum and thalamus indicating deep venous thrombosis with infarction and petechial change.

Figure 6 CT venogram showing filling defects within the superior sagittal sinus with complete lack of opacification of the posterior superior sagittal, straight and transverse sinuses (arrowed). There is extensive filling of collateral pial veins over both cerebral hemispheres.

Figure 7 Phase-contrast time-of-flight MRV showing absent transverse sinus (arrowed).
In some cases, magnetic resonance imaging (MRI) may be the initial radiological investigation. MRI has a higher sensitivity than CT in detecting thrombosis at each stage [35-36] and is superior to CT at visualising parenchymal oedema following CVT [33]. Clot within the cerebral veins replacing the normal “black” flow voids of the venous system may also be visualised on MRI, but interpretation requires detailed knowledge of the evolution of radiological findings of CVT as the dot signal intensities change depending on thrombus age and on the imaging sequence used [37-38]. Acutely (0-7 days), thrombus is isodense on T1-weighted images. On T2-weighted scans, signal from thrombus is hypodense compared to the brain and may be mistaken for normal flow voids. More recently, T2 gradient echo sequences which are sensitive to early clot breakdown products have been used to identify thrombus in the acute phase [39]. By week two abnormalities are easier to detect, with both T1 and T2 weighted images showing a hyperdense signal, due to methaemoglobin within the thrombus [33,38]. Other signs of CVT on contrast enhanced MRI include absence of sinus flow signal or enhancement around an isodense lesion analogous to the empty delta sign [40].

These complicated changes in image-intensity and susceptibility to slow and turbulent flow mean that while MRI has better sensitivity and specificity compared to CT, CVT cannot be excluded without diagnostic or confirmatory venous imaging [41]. This may be via CT venography (CTV) or MR venography (MRV).

MRI/MRV has been considered the gold standard for diagnosing CVT. However, with the advent of modern helical CT scanners, evidence has emerged indicating CTV is at least as sensitive for diagnosing CVT as MRV [33,41]. Thrombus on CTV is seen as a filling defect with contrast enhancement of the walls of the dural sinus. The ability to perform CTV rapidly after initial NECT with the patient still on the scanner makes CTV an attractive option for many departments, and the German Neurological Society guidelines indicate CTV and MRV as equivalent for CVT diagnosis. Drawbacks of CTV compared to MRV include contrast-related reactions, risk of contrast nephropathy and radiation exposure [42].

While different MRV techniques are available, phase-contrast time-of-flight MRV (TOF-MRV) is most commonly used [35,43]. 2-dimensional TOF-MRV is less prone to slow flow artefacts than 3-dimensional TOF [2]. Contrast enhanced MRV provides improved visualization of the small vessels compared to TOF-MRV and is less susceptible to false positives resulting from complex flow [44-45].

Digital subtraction angiography (DSA) had been the mainstay of diagnosis of CVT prior to the widespread use of MRI and CT imaging modalities. Despite having superior temporal and spatial resolution, the invasive nature of formal angiography means that DSA is now reserved for those cases where endovascular treatment is being considered or where other modalities are unable to confirm the diagnosis [2]. It is particularly helpful in identifying anatomical variants of normal venous anatomy mimicking sinus thrombosis. However, due to high variability in venous anatomy, direct signs of missed cortical veins are difficult to definitively image. Instead diagnosis relies on indirect signs such as a “corkscrew” collateral vessels and parenchymal vascular congestion [46].

**Laboratory investigation**

Because of the wide number of diagnoses that may mimic CVT, a simple screening test to rule out the diagnosis without resorting to neuro-imaging would be a boon to clinical practice. D-dimers have been examined in this role. In patients with papilloedema or encephalitic signs (local neurology, seizures, disturbances of consciousness) when the clinical suspicion of CVT is high, the sensitivity and specificity of the d-dimer is high [47]. However, in these cases, it is likely that patients will proceed to appropriate CVT imaging in any case. In the common clinical scenario of isolated headache, d-dimers have been shown to have unacceptably high false negative rates of up to 26%. There is also evidence that d-dimers may be even less sensitive for later presentations [47]. This low sensitivity is in contrast to their value in the diagnosis of deep vein thrombosis (DVT) and may be explained by a lower thrombotic burden in CVT compared to DVT [6,47-48]. Guidelines state that in those with a strong clinical suspicion of CVT, negative d-dimers should not prevent further imaging [2].

Another common clinical question relates to the nature and timing of thrombophilia testing. Guidelines recommend testing for factor V Leiden mutation, prothrombin gene mutation 20210, lupus anticoagulant and anticardiolipin antibodies, hyperhomocysteinemia, and deficiencies of protein C, S and antithrombin. However, some practical considerations must be borne in mind. Testing for deficiencies of protein C, S, and antithrombin must be done at least 6 weeks after clot formation. They should not be performed on patients taking oral anticoagulants (OACs) and must be done at least 2-4 weeks after cessation of these treatments (OACs increase antithrombin and dramatically reduce protein C and S). In addition heparin causes a decline in antithrombin.

Tests for the antiphospholipid antibody syndrome include an ELISA test for the anticardiolipin antibody and anti-ß2-glycoprotein I antibody and clotting studies for the lupus anticoagulant. Normal antibody testing at that time of presentation should be treated with caution, as a normal result may be found in those with the syndrome at this time. It should be repeated in those with a high clinical suspicion and those with a prolonged aPTT. If a positive antibody test is found, it is recommended that repeat testing be undertaken as transient elevations are common.

Other laboratory investigations recommended include blood count, renal profile, liver profile and coagulation screen. Inflammatory marker estimation is also recommended in assessing for the presence of a pro-coagulation inflammatory state [2].

**TREATMENT**

**General measures**

General supportive measures for patients with neurological pathology should be instigated. Airway integrity should be maintained and supported with intubation if at risk. Those patients with neurological deficits not needing organ support...
should be managed on a stroke unit with close monitoring as neurological deterioration may occur in up to a quarter of patients, even several days after diagnosis [12]. Specific causes of CVT such as infection should be found and treated and pro-coagulant medication such as the OCP should be discontinued.

Anticoagulation

An obvious treatment modality for CVT is anticoagulation with the aim of preventing thrombus propagation, promoting re-canalization and prevention of extra-cerebral VTE. However, anticoagulation is not straightforward in patients with CVT due to the high rates of hemorrhagic transformation of infarcts and spontaneous intracranial haemorrhage (ICH) leading to safety concerns.

The role of anticoagulation against placebo in the acute setting has been assessed in two small randomised controlled trials (RCTs) that have met Cochrane criteria. The first, involving 20 patients treated with unfractionated heparin (UFH), was stopped early due to the beneficial effects seen in the treatment arm [49]. The second used low molecular weight heparin (LMWH) in 59 patients [50]. Patients in the treatment arm had a favourable outcome more often than controls, although this difference did not reach statistical significance. Despite 50% of patients having intracranial bleeding on their initial scans in the treatment group, there were no new symptomatic ICH. A Cochrane review pooling these trials found a non-significant trend for reduced death rates with a relative risk (RR) 0.33 (95% CI, 0.08-1.21) and an RR of death or dependency of 0.46 (95% CI, 0.16-1.31) [51]. In a recent trial undertaken at a single centre in India, LMWH was compared to UFH in 66 patients. All 6 deaths that occurred within the hospital stay occurred in the UFH group (P = 0.01) [52]. On the basis of these trials, both European and American agencies recommend anticoagulation regardless of ICH, and in light of the recent study most physicians recommend LMWH over UFH. Nevertheless, the clinician may be confronted with circumstances in which the benefits and risks of anticoagulation may be very finely balanced. In these circumstances advice from specialists in haemostasis may be of benefit.

Having established the patient on heparin, most authors recommend oral anticoagulation with a vitamin K antagonist, aiming for an INR of 2-3. This is initiated when the patient stabilises or shows signs of improvement [53]. Most trials have started OACs at 14 to 21 days. Studies suggest that re-canalisation occurs in the first few months following CVT and not thereafter [54], and therefore the aim of long-term anticoagulation is predominantly to prevent recurrent thrombotic events.

There have been no trials examining the duration of anticoagulation in CVT and therefore the optimum time to continue anticoagulation is unknown. The rate of recurrence of CVT is low at approximately 2% and slightly higher for non-cerebral VTE at 3% in ISVST [55-56]. Longer term VTE recurrence is higher after anticoagulation withdrawal at 35.1 events/1000 patient-years [57]. Although the rate of any thrombotic event post CVT is lower than that following lower limb DVT [57-58], many clinicians use extrapolation of VTE studies to inform decision on oral anticoagulation.

According to guidelines from both American and European agencies, the duration of anticoagulation will depend on the presence of ongoing risk factors. For CVT attributable to a transient risk factor e.g. pregnancy or infection, anticoagulation is recommended for 3 to 6 months. In those patients without a transient risk factor, the clinician must weigh up benefits of preventing further VTE against the bleeding risk associated with anticoagulation. The HAS-BLED tool provides a risk estimate for major bleeding according to patient specific risk factors for patient on OAC, although overall incidence for major bleeding per year is 1-2% [59].

Both American and European guidelines also recommend differentiating those with “mild” (homozygous factor V Leiden or prothrombin G20210A mutation) and “severe” thrombophilia (antithrombin, protein C or protein S deficiency, homozygous factor V Leiden or prothrombin G20210A mutation, antiphospholipid antibodies and combined abnormalities) based on VTE recurrence rates in large family cohorts. Those with mild thrombophilia should be anticoagulated for a period of 6-12 months and those with severe thrombophilia anticoagulated indefinitely. This approach is supported by a study of 145 patients attending a thrombophilia clinic who were followed up for a median of 6 years. Those patients who were classed as having a mild thrombophilia were not at increased risk of developing recurrent venous thrombosis, whereas those with severe thrombophilia were more likely with an hazard ratio of 4.71 (95% CI, 1.34 to 16.5) [55].

It should be noted that these CVT specific guidelines differ to those on the management of VTE. These indicate lifelong therapy in patients with idiopathic and recurrent VTE, especially those with a low bleeding risk and a low risk of developing thrombosis (usually 3-6 months) to those with transient risk factors [60-61]. In addition, another large multicentre study found that predictors of recurrent VTE do not include thrombophilic states, with only previous VTE independently predicting recurrence [57]. The presence of inherited thrombophilia may be lower in CVT than thrombosis in other venous systems [19]. Therefore the role of diagnosis of inherited thrombophilic states is controversial, as knowledge of an inherited thrombophilia may not influence treatment decisions in unprovoked CVT or VTE.

Patients with cancer present another specific clinical circumstance. This group has particularly high risk of both recurrent VTE and bleeding complications. A large multicentre RCT has shown a reduction of recurrent VTE with LMWH over warfarin at 6 months [62]. However, the burden of long-term daily injections may limit the use of LMWH. As such, these patients should be treated with LMWH for 3 months followed by discussion regarding the merits of continuing injections against OACs.

Pregnant patients also differ in their management. Vitamin K antagonists are contra-indicated in pregnancy and LMWH is the anticoagulant of choice. The prothrombotic state of pregnancy continues for at least 4 weeks post partum, and so the American College of Chest Physicians recommend extending anticoagulation for 6 weeks post partum and for a minimum total of 6 months. The rate of recurrence of CVT in pregnancy is very low and CVT is not seen as a contraindication of future pregnancy, although LMWH prophylaxis is recommended [53].
Intravenous re-canalisation

Despite outcomes better than those seen in arterial stroke, certain sub-groups of CVT have a poor recovery. Approximately one third of patients will present with features placing them at high risk of death or permanent disability. In ISVST, 40% of patients whose presentation was complicated by a mental status disorder, coma or thrombosis of the deep venous system had died or were physically disabled at 6 months [7]. Recently, focus has intensified on improving outcomes in this group by improving rates of venous re-canalisation using endovascular techniques. A catheter is advanced to the site of the thrombus via the jugular or femoral vein and thrombolytic agents applied to the thrombus in combination with mechanical clot disruption.

This method has a number of theoretical advantages, including faster rates of re-canalisation and application of thrombolytic drugs only to the site of thrombus and downstream of vascular congestion at risk of hemorrhagic transformation. Evaluation has so far been only through case reports and case series, limiting the conclusions that can be drawn about the safety and efficacy of these procedures. Indeed, indications as to the efficacy of endovascular treatments from these reports are conflicting. A 2003 systematic review showed a similar mortality in patients undergoing endovascular interventions patients in large prospective case registries despite clinical indicators of more severe disease [63]. However, concerns over publication bias have been highlighted by data from a prospective case series indicating death and dependency in 40% [64]. Those patients with impending cerebral herniation have a particularly poor outcome, with the authors recommending hemicraniectomy in such cases [64]. A multicentre RCT is underway comparing endovascular thrombolysis and standard anticoagulant treatment in patients with a poor prognosis [65]. Current guidelines recommend its use in selected patients where anticoagulation has been deemed to have failed and who do not have ICH or impending herniation from large haemorrhagic infarcts [1]. There is no consensus on the optimum device, route, thrombolytic drug or method of administration.

TREATMENT OF COMPLICATIONS

Seizures

Seizures are common in CVT with 39% of patient presenting with this complication in ISCVT and a 6.9% developing early seizures (<2 weeks from diagnosis). Anticonvulsants are recommended promptly after their occurrence to prevent possible metabolic deterioration. Results from uncontrolled case registries indicate that in patients presenting with seizure and supratentorial lesions, prescription of antiepileptic drugs (AEDs) reduces the risk of further seizures [28]. Supratentorial lesions also predict early seizure, but the use of prophylactic AED in this group is controversial, with guidelines recommending against routine administration. Most late seizures (defined as >2 weeks after diagnosis and occurring in 11% of patients in ISCVT) happen within 12 months, and there is a low longer term risk [66]. It is therefore reasonable to continue AED for at least one year [27].

Treatment of intracranial hypertension

CVT is often complicated by intracranial hypertension. In severely elevated intracranial hypertension, general measures to reduce pressures are indicated. These include raising the head of the bed, treatment with mannitol, intubation and sedation with hyperventilation and invasive intracranial pressure (ICP) measurement. Steroids are not recommended. Evidence for their lack of efficacy comes from the ISCVT cohort [67]. Using case-control methodology, no significant benefit was found in patients treated with steroids. In addition, patients without parenchymal lesions had worse outcomes.

The modality of death in patients with CVT is principally through cerebral herniation and so surgical decompression may be life saving [68]. This option has been explored in published reports and case series. A combined retrospective registry and systematic review of published cases identified 69 surgically treated cases, 45 of whom had hemicraniectomy and 17 who had hemicraniectomy combined with hematoma evacuation [69]. At a median of 12 months follow up, 37.7% of patients were independent with a modified Rankin Scale (mRS) of 0-1, and 17.4% had an unfavourable outcome with a mRS of 4-6. The majority of patients had a severe condition with signs of impending herniation. The authors concluded that even with large lesions causing herniation, surgery could be life saving and result in a good functional outcome.

In patients with chronically raised ICP, vision is at risk. Papilloedema must be sought and an assessment of vision undertaken including visual fields. In those with threatened vision and no contraindications to lumbar puncture (LP), this procedure is diagnostic of elevated ICP and therapeutic removal of fluid to obtain a normal closing pressure will usually result in rapid improvements in headache and vision [12]. Anticoagulation may be started 24 hours post procedure [1]. Although not of proven efficacy, oral acetazolamide (500 to 1000 mg daily) may reduce ICP. If repeated LP is required, shunting procedures should be considered [1].

Obstructive hydrocephalus is a less common complication of CVT, occurring in approximately 1% of patients [70-71]. It occurs when there is obstruction of either the foramen of Monro, the aqueduct of Sylvius, or at the fourth ventricle, either from external compression from haemorrhage or oedematous parenchyma or from blood within the ventricular system. It is treated in a standard neurosurgical manner with external ventricular drainage or posterior fossa decompression.

A large body of evidence supports the provision of care for patients with ischaemic or haemorrhagic stroke on dedicated stroke units staffed by coordinated teams of physicians, nurses and therapists with a specialist interest in stroke. Stroke unit care compared to contemporary conventional care in general wards results in reduced death, dependency and institutionalization [72]. With these benefits being independent of stroke sub-type, guidelines suggest that patients with CVT (and especially those with neurological deficits) should be cared for on stroke units.

PROGNOSIS

CVT has more favourable prognosis than arterial or haemorrhagic stroke. Most deaths occur early from cerebral herniation as a consequence of focal mass effect from large infarcts of haemorrhages or diffuse brain oedema from multiple
lesions. In Dental’s meta-analysis, 30 day mortality was 5.6%. At 1 year follow up, most deaths occur due to an underlying disorder (usually cancer) rather than CVT itself [54]. Good neurological outcome defined by complete or partial recovery with a mRS of 0-1 was found in 79% at one year in ISCVT, with 5% of patients surviving with a moderate to severe disability.

Consistent predictors of dependence and death at 12 months have been older age (>37 in ISCVT), coma at presentation (GCS<9), worsening of neurological status, seizures, ICH and cancer [54]. Patients with isolated intracranial hypertension have a more favourable prognosis with 7.7% dead or dependant at a median 16 months follow up compared to 13.6% for other patients [7].

Partial or complete re-canalisation occurs in approximately four fifths of patients at one year, with the vast majority occurring early and within 3 months [58]. No studies have shown a correlation between re-canalisation rates and clinical outcomes [74].

FUTURE RESEARCH

In this rare disease, research networks have proved invaluable in facilitating adequate patient recruitment to allow the expansion of a body of evidence, informing treatment decisions in CVT. Despite this, considerable uncertainty remains. Ongoing RCTs investigating the role of endovascular thrombolytic techniques will inform clinical practice. The new generation of oral anticoagulants has shown non-inferiority in stroke prevention in atrial fibrillation and in VTE treatment compared to warfarin with distinct advantages including not requiring laboratory monitoring. The duration of anticoagulation is unclear and there is a need for clinical trials to assess the efficacy and safety of short versus extended anticoagulant therapy. D-dimers may have a role to play in disease monitoring and informing long term anticoagulation decisions. AED prophylaxis is controversial and may be amenable to large clinical trials. Finally, it is not only treatment modalities where research opportunities exist with advancing technology providing avenues for improved diagnostic speed and accuracy.

CONCLUSION

In summary, CVT represents a diverse and clinically challenging condition. Recent research has advanced the understanding of disease processes, enabled more accurate diagnosis and defined effective treatment modalities, and with modern therapy patients have a favourable prognosis. However, a sub-group of patients with poor prognostic features have adverse outcomes with a high risk of morbidity and death. Aggressive treatment with surgery and endovascular procedures may still allow excellent recovery in this group.

REFERENCES


