
بسم الله الرحمن الرحيم

Cerebral venous thrombosis: a practical guide

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- All neurologists need to be able to recognise and treat cerebral venous thrombosis (CVT).
- Although CVT can result in death or permanent disability, it generally has a favourable prognosis if diagnosed and treated early.

- Cerebral venous thrombosis (CVT) is an important cause of stroke in young adults(mean age 33 years with a two-thirds female).

- caused by complete or partial occlusion of the cerebral major cerebral venous sinuses or the smaller feeding cortical veins.
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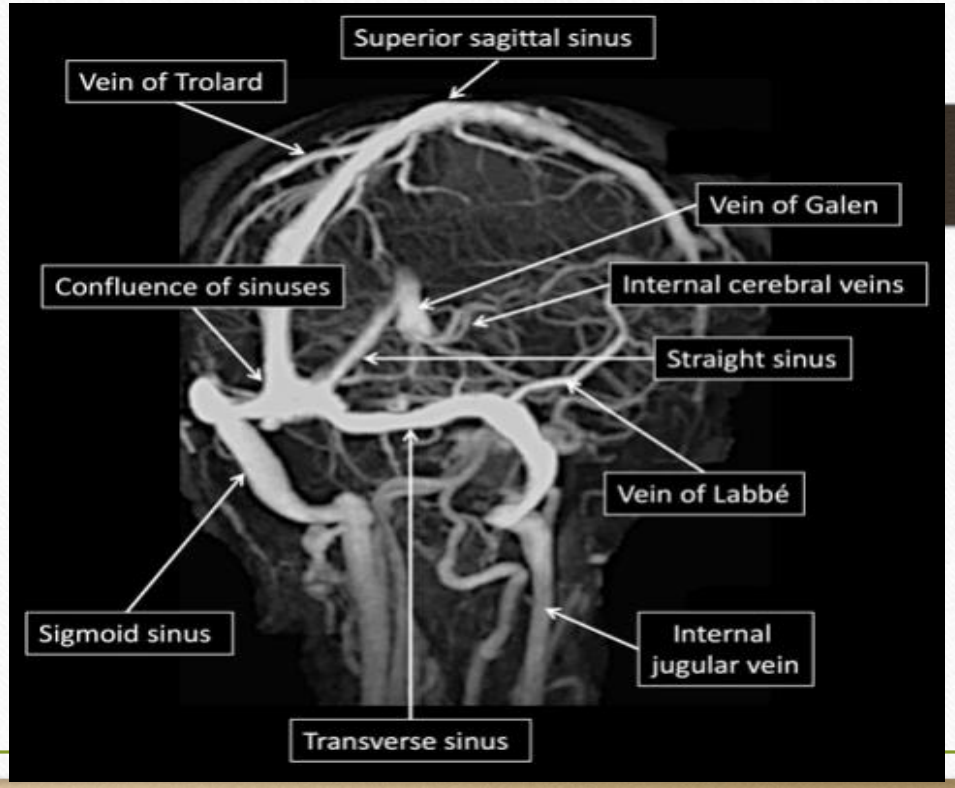
- CVT is frequently missed or diagnosed late because it can mimic other acute neurological conditions and can only be recognised with optimal and timely brain imaging.

- CVT generally has a favourable prognosis if diagnosed and treated early.
- 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).

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

pathophysiology

Blood from the brain drains through small cerebral veins into larger veins of the deep venous system (including the
internal cerebral veins, basal veins (of Rosenthal) 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.



Virchow's triad:

- Changes in blood stasis,
- vessel wall abnormalities
- and the composition of the blood

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 thus, both cytotoxic and vasogenic oedema can occur.

. CVT can also block cerebrospinal fluid absorption through the arachnoid villi, which then leads to raised intracranial pressure, 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.

Occluded sinus/ vein	Clinical presentation
Transverse sinus (44–73%)	If isolated without infarction: asymptomatic or headache Seizures Contralateral pyramidal symptoms and signs If left transverse sinus with venous infarction and vein of Labbé occlusion: aphasia If extending into the contiguous sinuses: intracranial hypertension, consciousness disturbance, focal cerebral signs and cranial nerve palsies (IX-XXI) If extending into the cerebellar veins: headache, vomiting, and limb or gait ataxia.

Superior sagittal sinus (39–62%)	Isolated intracranial hypertension Focal symptoms due to venous infarction (see below) Isolated psychiatric symptoms (rare) ▶ Headache ▶ Blurred vision ▶ Visual loss ▶ Nausea, vomiting ▶ Cranial nerve palsy (differential diagnosis of pseudotumor cerebri) ▶ Aphasia ▶ Hemianopia ▶ Hemisensory loss and/or hemiparesis ▶ Seizures

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 symptoms and 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)

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 even months.

Table 2 Risk factors for cerebral venous thrombosis (from Ferro *et al*[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 prothrombotic condition (thrombophilia)	22.4% / 15.7%
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.
Intravenous immunoglobulin	n.d
Ecstasy	n.d
Vascular abnormalities	
Dural arteriovenous fistulae	1.6%
Arteriovenous malformations	0.2%
Other venous abnormalities	0.2%

- The International Study on Cerebral Vein and Dural Sinus Thrombosis 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)

- Headache is the most common symptom of CVT, reported in about 90% of cases; indeed, it is the only manifestation in about 25% of patients.

- 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.

- Headache from CVT can be localised or diffused, sometimes with migrainous headache or aura features.

Table 3 When to suspect CVT in a patient with headache

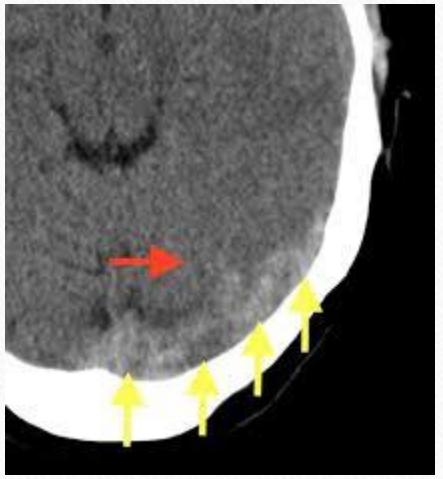
Presence of CVT risk factors (eg, oral contraceptive, pregnancy or puerperium, malignancy, anaemia)
New headache or head pain with different features in patients with previous primary headache
Symptoms or signs of raised intracranial pressure (eg, papilloedema)
New focal neurological signs
Altered consciousness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

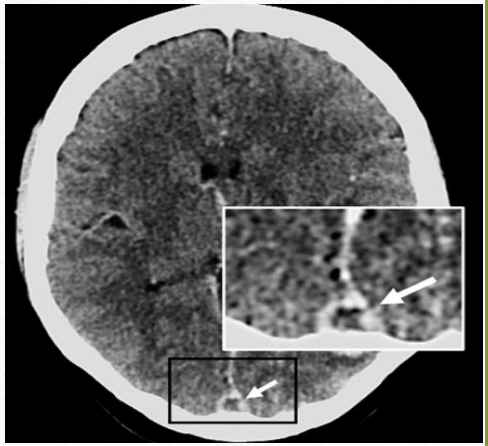
Stroke-like focal neurological symptoms occur in up to 40% of patients with CVT, though are often not as sudden in onset as arterial ischaemic stroke or intracranial haemorrhage; motor symptoms are most frequent, followed by visual impairment and aphasia (especially if the left transverse sinus and vein of Labbé are involved),whereas sensory symptoms are less common.

DIAGNOSIS

Non-contrast CT scan of head is a useful first test (and the first brain imaging in suspected stroke or acute headache in many hospitals): in about one-third of patients, it shows specific signs including venous sinus or deep vein hyperdensity, Sometimes termed the dense triangle sign (high attenuation in the sagittal sinus or deep cerebral veins in a triangle shape) or the cord sign (high attenuation due tothrombus in the transverse sinus).

However, plain CT is normal in up to 30% of patients and, even if abnormal, is not specific.
Thus, all patients with suspected CVT require further imaging beyond a plain CT scan.





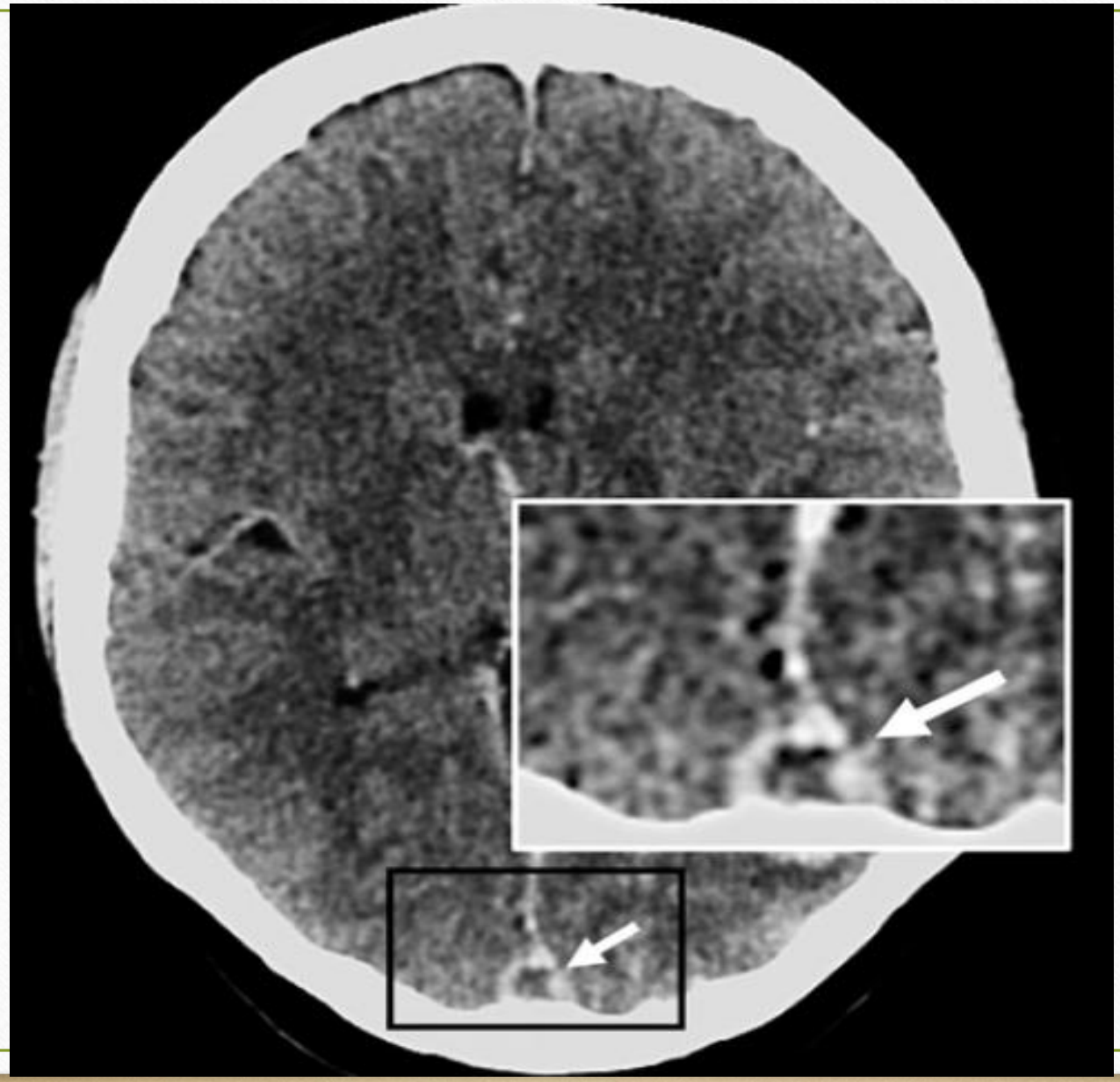
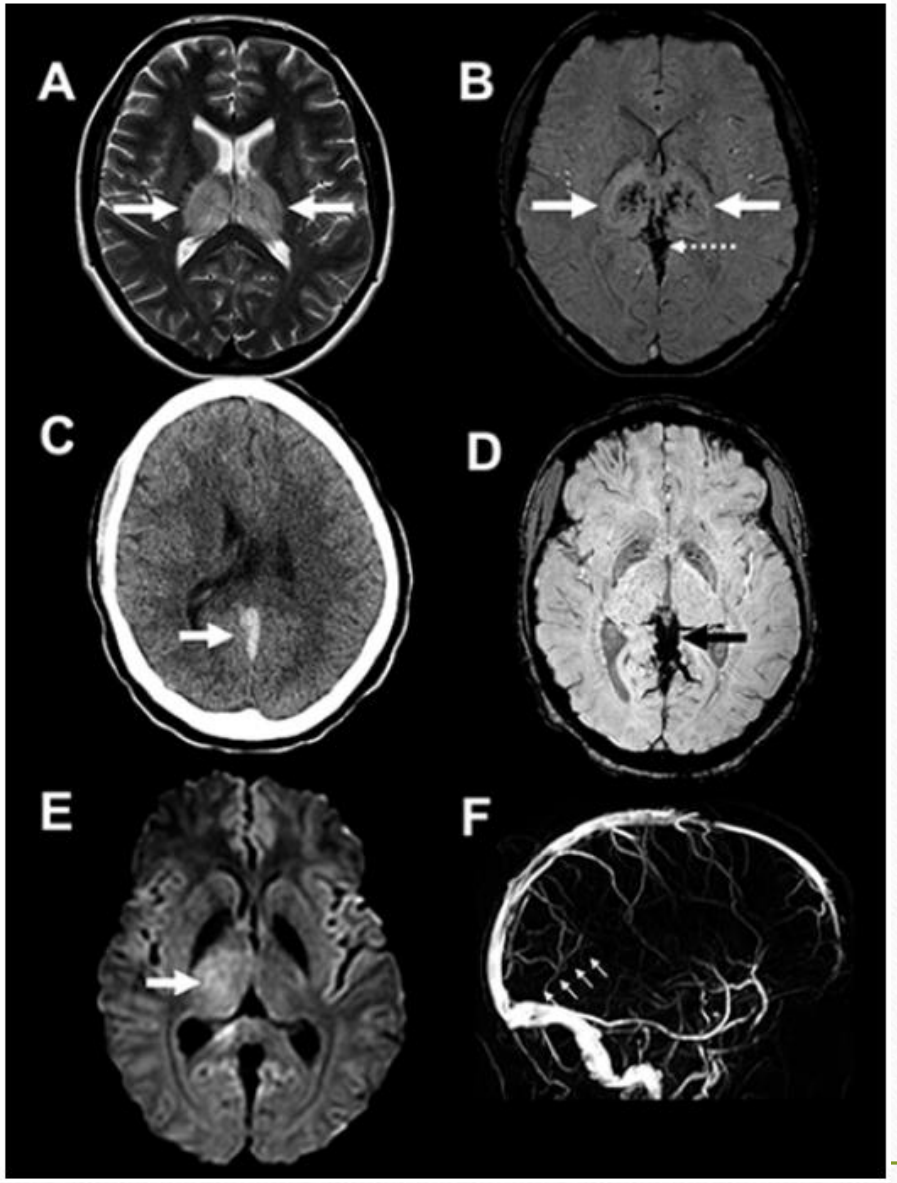


Table 4 Neuroradiological features of CVT

	CT + CT venography	MR + MR venography
Typical findings	Sinus or vein hyperdensity Dense triangle sign Empty delta sign Cord sign Absence of flow in thrombosed sinuses	1 week: isointense on T1 and hypointense in T2W images 2 weeks: hyperintense on T1 and T2W images >2 weeks: variable on T1 and T2, hypointense in GRE and SWI DWI hyperintensity Venous wall enhancement Absence of flow in thrombosed sinuses

Advantages	Easily available Fast Reduced motion artefact	No ionising radiation exposure No contrast medium required Good visualisation of brain parenchyma Good for detection of cortical and deep cerebral vein thrombosis
Disadvantages	Ionising radiation Use of contrast medium Poor detection of small parenchymal abnormalities Low sensitivity in small cortical and deep thrombosis	Time consuming Motion artefact can degrade images Reduced availability Contraindicated in some patients (eg, cardiac devices, medically unstable)

Figure 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 haemorrhage 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). SWI, susceptibility-weighted imaging.



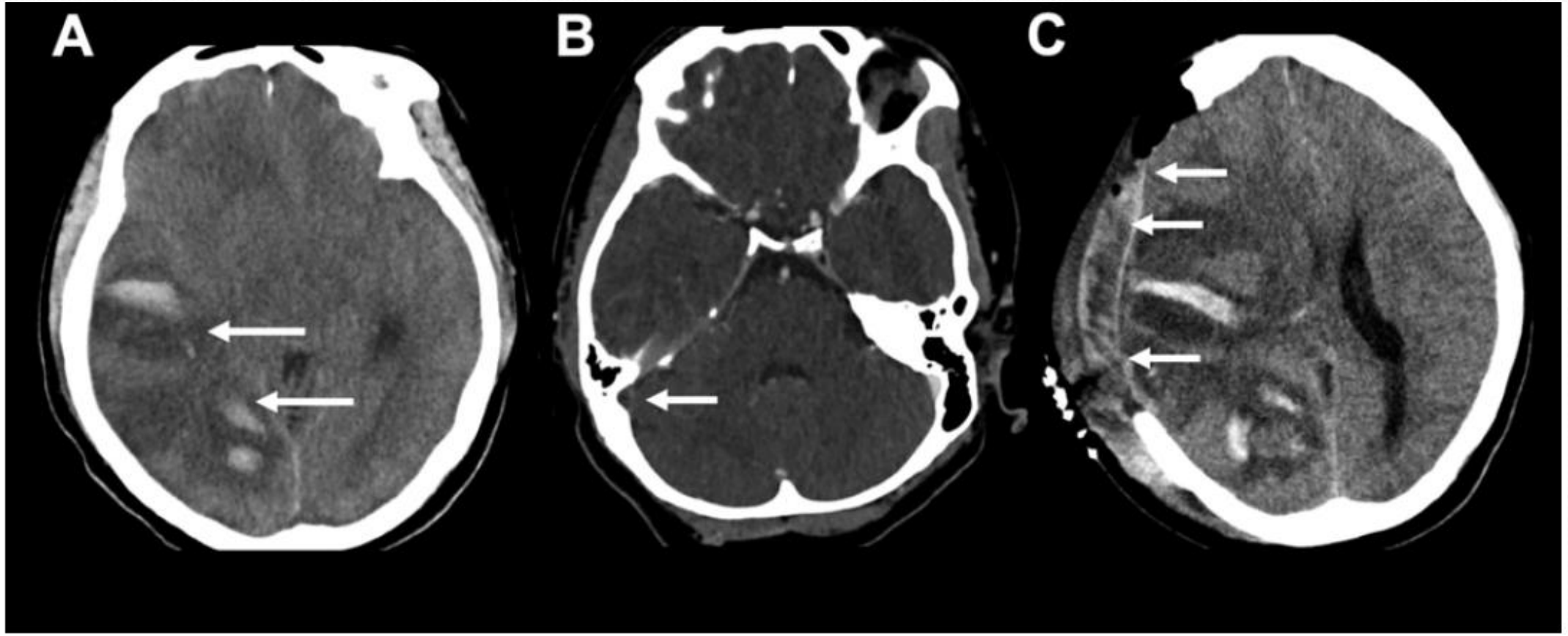


Figure 3 Transverse venous sinus thrombosis. (A) Area of haemorrhagic infarction of the right temporoparietal region not respecting arterial boundaries with swelling and oedema (white arrows); (B) CT venogram showing absent contrast filling of the right transverse sinus (white arrow); (C) severe haemorrhagic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

MRI is the most sensitive technique for demonstrating the presence of the thrombus material, using sequences sensitive to the magnetic susceptibility effects of para magnetic iron-containing blood components (T2*-weighted gradient echo or susceptibility-weighted imaging; SWI.

the appearance of the clot on different MRI sequences varies depending on its age so can also help to date likely CVT onset.

MRI is also the best technique to assess parenchymal involvement fully (ischaemia, haemorrhages, oedema, swelling)

Catheter intra arterial DSA should be used to confirm the diagnosis only when CT venography or MR venography is inconclusive or there is a suspicion of adural arteriovenous fistula.

Isolated cortical vein thrombosis is usually well seen on susceptibility-weighted sequences but can be challenging diagnose, and occasionally also requires intra-arterial DSA to confirm.

TREATMENT

Treatment should be started as soon as the diagnosis of CVT is clearly confirmed, with rapid anticoagulant therapy, treatment of any underlying cause (eg, dehydration, sepsis, stopping any prothrombotic medications), control of seizures and management of intracranial hypertension if required.

Anticoagulation

The evidence supporting anticoagulation in CVT is widely accepted and guides clinical practice.

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 with a lower risk of major bleeding or death.

We very rarely use unfractionated heparin as it is very difficult to monitor and ensure therapeutic anticoagulation.

Although there are no large, high-quality randomised trials, LMWH is recommended in guidelines from the ESO and is our standard practice; we usually give this as split-dose (ie, two divided doses per 24 hours)to minimise the risk of haemorrhagic complications.

The ESO guidelines advises that unfractionated heparin should be used in patients with renal insufficiency or in patients requiring very rapid reversal of anticoagulation (eg, imminent neurosurgical intervention).

However, the summary of product characteristics for LMWH do not include severe renal impairment as a contraindication.

Cortical vein thrombosis is also usually treated with anticogulation (and is our practice) though there are no randomised controlled trials.

Preventing further venous thrombotic events

- Initial anticoagulation with LMWH (started as soon as the diagnosis is confirmed) is followed by 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 4–7% per year.
- 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 3and 12 months.

patients with one episode of CVT and transient risk factors (dehydration, drugs (eg, oral contraceptives), infections, trauma, surgical interventions) should receive anticoagulation for 3–6 months.

patients with one episode of CVT of unknown cause should continue anticoagulation for 6–12 months.

and 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.

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.

However, current guidelines do not recommend DOACs in patients with CVT because of the limited quality of the available evidence.

Endovascular treatment

While anticoagulation aims to prevent the progression of the thrombus 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 it.

ESO guidelines recommend that endovascular treatment should only be considered in patients with a high pretreatment risk of poor outcome.

Treatment of elevated intracranial pressure

In the acute phase of CVT, elevated intracranial pressure (due to space-occupying brain oedema, infarction, intracranial haemorrhage) and brain herniation can rapidly lead to severe brain injury and death.

Medical therapy for elevated intracranial pressure includes osmotic therapy (such as mannitol), hyperventilation (PCO2 30–35 mmHg) and elevating the head of the bed.

Therapeutic lumbar puncture has been proposed to reduce intracranial pressure in patients with CVT and isolated intracranial hypertension, 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

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(Behçet's disease, systemic lupus erythematosus).

In the 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.

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%

ESO-EAN strongly recommend decompressive hemicraniectomy in otherwise well patients with parenchymal lesion(s) and impending herniation

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 cerebralartery territory.

A persistent intracranial pressure >20 cmH2O is also suggested as a criterion for surgery

The optimal timing of anticoagulation after hemicraniectomy is not clear, being reported between 24 hours and 8 days.

The bone flap is often replaced after 3–6 months, when the brain swelling resolves.

Ventricular shunting does not appear to prevent death or herniation, so is not recommended to treat raised intracranial pressure in CVT.

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 appropriate.

- 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.
- Our practice is generally to treat only those with clinical evidence of seizures.
- When seizures are treated, it is important to avoid antiepileptic drugs that interact with the planned anticoagulant treatment.

There is no evidence about to ptimal duration of treatment. We base our practice on current data that suggest for seizures associated with oedema, infarction or haemorrhage, treatment should be continued for at least 1 year.

PROGNOSIS

CVT generally has a favourable outcome, with a complete functional recovery reported in about 75% of patients; however, about 15% die or are dependent

risk factors for a **poor outcome include**:
male sex, **older age**, confusion or coma, **intracranial haemorrhage**, deep vein involvement**, infection and malignancy**

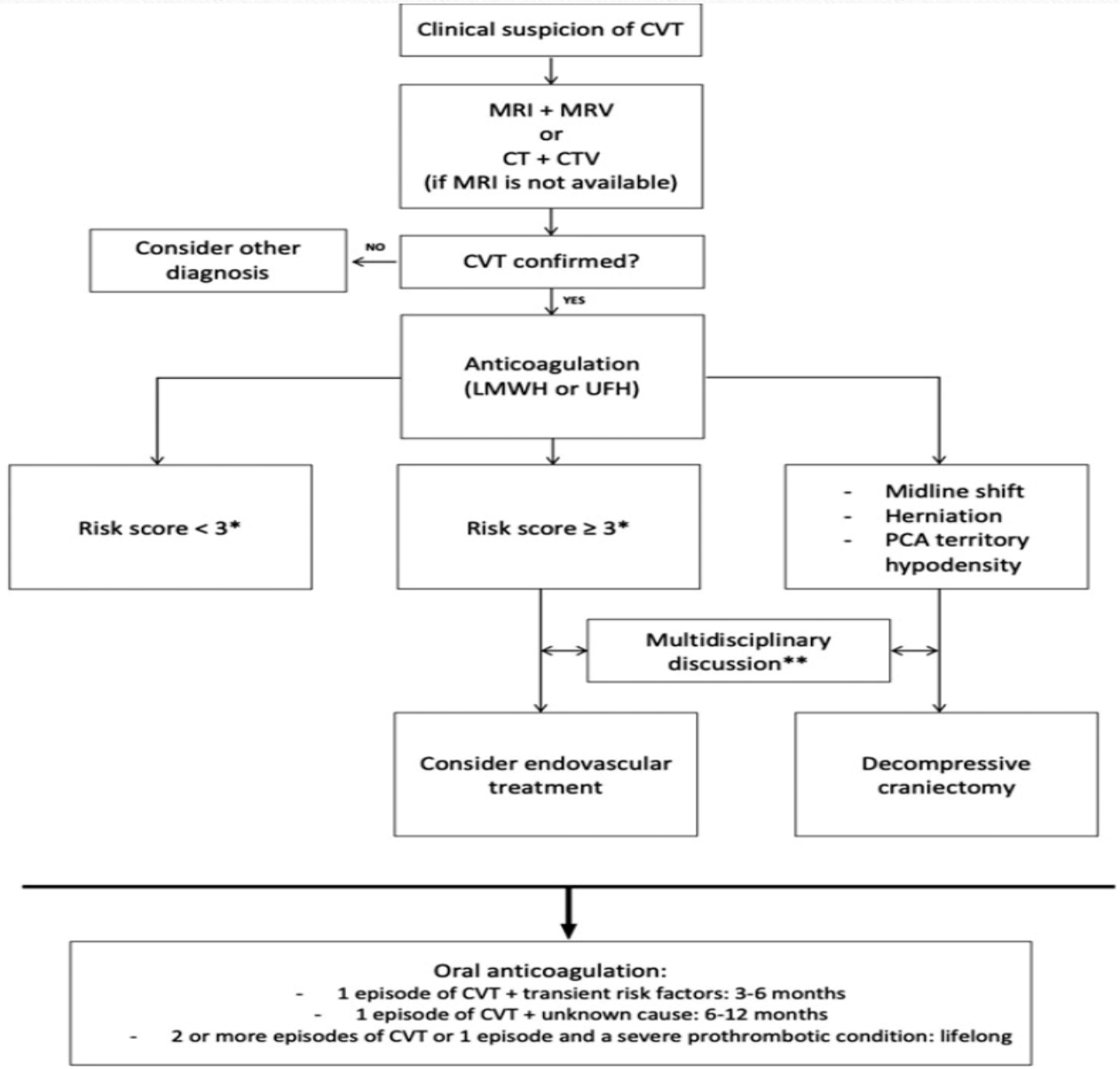
Despite good physical recovery, many survivors have symptoms of depression or anxiety, or cannot return to work because of cognitive impairment. Cognitive decline is under-investigated and under-recognised, especially when deep veins are involved, where it is reported in up to one-third of patients.

Table 5 Prognostic score for CVT[60]

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.[53]



Key points

- Cerebral venous thrombosis (CVT) is a rare but important cause of stroke in young adults; its diagnosis is challenging because of the many and varied symptoms, and depends on rapid and appropriate neuroimaging.
- Once CVT is diagnosed, it is essential to make a careful search for an underlying cause, for example, oral contraceptive use or thrombophilia (genetic or acquired).
- The treatment includes anticoagulation with parenteral heparin, prevention of recurrent seizures, and decompressive neurosurgery in patients with large space-occupying venous infarction, haemorrhage or both; the role of endovascular therapy remains unproven.
- Anticoagulation is generally recommended for 3–12 months or longer depending on the estimated risk of recurrence; direct oral anticoagulants are a promising alternative to warfarin, but we await further trial data.


با تشکر از توجه
شما