

Cerebral venous thrombosis

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Abstract | Cerebral venous thrombosis (CVT) is an important cause of stroke in young adults. Data from large international registries published in the past two decades have greatly improved our knowledge about the epidemiology, clinical manifestations and prognosis of CVT. The presentation of symptoms is highly variable in this disease, and can range from a patient seen at the clinic with a 1-month history of headache, to a comatose patient admitted to the emergency room. Consequently, the diagnosis of CVT is often delayed or overlooked. A variety of therapies for CVT are available, and each should be used in the appropriate setting, preferably guided by data from randomized trials and well-designed cohort studies. Although deaths from CVT have decreased in the past few decades, mortality remains ~5–10%. In this Review, we provide a comprehensive and contemporary overview of CVT in adults, with emphasis on advancements made in the past decade on the epidemiology and treatment of this multifaceted condition.

In 1825, the French physician Ribes reported a case of a 45-year-old man who experienced headache and seizures; autopsy revealed that these symptoms were caused by thrombosis of the superior sagittal and lateral sinuses^{1,2}. This case report constitutes the first detailed description of a patient with cerebral venous thrombosis (CVT). A few years later, an association was found between CVT and pregnancy — or more precisely, puerperium — for the first time: John Abercrombie, physician to King George IV, reported a case of a 24-year-old woman who, 2 weeks after an uncomplicated delivery, developed a headache and multiple seizures³. This patient died as a result of status epilepticus, and autopsy revealed thrombosis of the superior sagittal sinus and cortical veins. In the subsequent decades, many case reports and small case series of CVT were produced, but it was not until the second half of the 20th century, after the introduction of catheter cerebral angiography, that larger clinical studies were published, which greatly advanced our knowledge of the clinical manifestations of and risk factors for this condition^{4–8}. The widespread availability of CT with venography in the late 1980s, and of MRI with venography several years later, enabled early non-invasive diagnosis of CVT^{9,10}. In the past two decades, findings have been published from large international registries from all over the world containing data from hundreds of patients with CVT^{11–14}. In this Review, we will provide a comprehensive and contemporary overview of the epidemiology, pathophysiology, diagnosis and treatment of CVT in adults. Paediatric CVT, which mostly concerns neonates, is beyond the scope of this Review¹⁵.

Epidemiology

Incidence. Early estimations of the incidence of CVT were based on autopsy series¹⁶. Extrapolation from an estimated mortality of 20–50% among patients with CVT at the time of these series gave an incidence of 0.1–0.2 cases of CVT per 100,000 people. However, data from population-based studies conducted in the past few years in the Netherlands and Australia have shown that the current incidence among adults is about tenfold higher than this estimate (1.3–1.6 per 100,000)^{17,18}, and the incidence is probably even higher in Asia and the Middle East, as the rates of pregnancy and infection-related cases are higher in these countries^{19,20}. Although the increase in incidence might partly be explained by a shift in risk factors, improvements in imaging techniques — which result in the identification of less-severe cases — is probably the most important contributing factor.

Risk factors and associated conditions. Most adults with CVT are aged 20–50 years and <10% of these individuals are older than 65 years²¹. Among young and middle-aged adults, CVT is threefold more common in women than in men. This heavily skewed sex ratio is the result of the sex-specific risk factors of oral contraceptives, pregnancy and puerperium^{22,23}. The risk of CVT in women who use oral contraceptives is increased approximately sixfold, and this risk is increased further still in women with obesity who use oral contraceptives²⁴. A large number of other risk factors — both transient and permanent — have been associated with CVT (TABLE 1). Many of these conditions, such as genetic thrombophilia, inflammatory disorders and cancer, are risk factors for venous

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doi:10.1038/nrneurol.2017.104
Published online 18 Aug 2017

Key points

- Cerebral venous thrombosis (CVT) is an important cause of stroke in young and middle-aged adults, with a sex ratio heavily skewed towards women
- Manifestations of CVT can be grouped into four distinct clinical syndromes: isolated intracranial hypertension, focal syndrome, diffuse encephalopathy and cavernous sinus syndrome
- First-line treatment for CVT is heparin, even in the presence of an intracerebral haemorrhage
- In a trial completed in 2017, endovascular therapy did not improve the clinical outcome of patients with severe CVT
- Mortality among patients with CVT has declined in the past few decades to ~8–10%; although 80% of patients recover without physical disability, many experience residual chronic symptoms

thrombosis in general. An association between CVT and the most common genetic risk factors for thrombophilia has been demonstrated in controlled studies²⁵. Conditions that specifically increase the risk of CVT include head trauma, arteriovenous malformations, neurosurgical procedures and infections of the head and neck^{26,27}. Notably, the prevalence of the risk factors varies considerably between countries. Dehydration, pregnancy and puerperium, and infections are all prominent causes of CVT in Asian and Middle Eastern countries, but are present in fewer than 15% of patients with CVT in large international and European registries^{11–13,19,28}. In Mediterranean and Middle Eastern countries, Behçet disease is an important cause of CVT²⁹. Overall, an associated condition can be identified in about 85% of patients^{11,13}.

Pathophysiology

CVT is caused by systemic or local imbalances in prothrombotic and thrombolytic processes, which lead to thrombus initiation and propagation in the cerebral dural sinuses or veins. As venous blood is forced back into small vessels and capillaries, an increase in venous and capillary pressure occurs^{30,31}. The specific anatomy of the brain venous system (FIG. 1), with its extensive anastomoses, often provides sufficient collateral circulation to compensate for such changes in pressure^{32,33}. However, when recruitment of collateral pathways does become insufficient, a disruption of the blood–brain barrier and decrease in cerebral perfusion pressure develops, which leads to cerebral oedema, local ischaemia and often intracerebral haemorrhage^{30,34,35}. Evidence for progressive hypoperfusion in experimental models of CVT, demonstrated by laser Doppler flowmetry and serial PET imaging, further supports the hypothesis that perfusion of the affected brain tissue is still possible in the initial phases of CVT through collateral drainage pathways^{32,33}. However, a 2015 study could not demonstrate an association between the extent of baseline intracranial venous collaterals and the clinical severity or prognosis in patients with CVT³⁶. Parenchymal lesions in CVT have frequently been suggested to occur only when the thrombus extends into the cortical veins, but studies in animal models indicate that occlusion of the major sinuses can be sufficient to cause venous infarcts^{33,37}. Parenchymal

lesions occur in ~60% of patients with CVT and differ considerably from those that occur in arterial stroke, as they cross arterial boundaries, have a haemorrhagic component in almost two-thirds of cases, and often consist of a combination of vasogenic and cytotoxic oedema^{11,38–40}.

In addition, the dural sinuses play a vital part in cerebrospinal fluid absorption. This process is mediated by the arachnoid villi (also known as Pacchionian granulations) that are found in the walls of the sinuses^{41,42}. Dysfunction of these granulations results in decreased cerebrospinal fluid absorption and subsequently to intracranial hypertension⁴³.

Clinical manifestations and diagnosis

Illustrative case history. A 40-year-old woman was admitted to the emergency room with a generalized convulsive seizure. For the previous few days, she had been complaining of a severe headache. At neurological examination, she opened her eyes on verbal appeal, made incomprehensible sounds, and localized to pain with her left arm. In the emergency room, she experienced four additional generalized convulsive seizures. CT imaging revealed an intracerebral haemorrhage (ICH) in the left frontal lobe, with perifocal oedema and sulcal subarachnoid haemorrhage (FIG. 2a). CT venography revealed thrombosis of the superior sagittal and left transverse sinus. The patient was started on low-molecular-weight heparin (LMWH) and antiepileptic drugs. After 4 days, her clinical condition deteriorated and she became comatose. Repeated neuroimaging showed progressive left-sided oedema and radiological signs of transtentorial herniation (FIG. 2b), at which point she underwent emergency, left-sided, decompressive hemicraniectomy (FIG. 2c). After surgery, she regained consciousness, but aphasia and hemiparesis remained. However, after 6 months, she had completely recovered without any residual functional disabilities.

Clinical manifestations. The symptoms presented by patients with CVT are highly variable (BOX 1). Severe headache is the most common and, usually, the first symptom of CVT, and is reported by 60–90% of patients^{11,12,19,44,45}. Some patients report thunderclap headache that mimics subarachnoid haemorrhage⁴⁶. Acute symptomatic seizures — that is, seizures that occur within 2 weeks of the diagnosis — are present in 30–40% of patients, which is a markedly higher proportion than seen in the acute phase of arterial stroke (2–9%) or spontaneous ICH (8–14%)^{47–53}. About 80% of acute symptomatic seizures actually occur before the diagnosis has been established⁵⁴.

Most patients present with a constellation of signs and symptoms that can be grouped into four distinct patterns^{26,55}. Patients with isolated intracranial hypertension experience headache (often accompanied by nausea), papilloedema, decreased visual acuity, and tinnitus. Second, patients with thrombosis of the superficial venous system and parenchymal lesions generally present with focal neurological deficits, often in combination with seizures. Thrombosis of the deep venous system with bilateral oedema of the basal ganglia and

thalami leads to mental status disorder, gaze palsy, diffuse encephalopathy, or coma. In rare cases, deep CVT can present with movement disorders⁵⁶. Finally, thrombosis of the cavernous sinuses results in orbital pain, chemosis, proptosis and ophthalmoplegia^{26,55}.

Laboratory investigations. Routine laboratory tests — including complete blood count, chemistry panel, urinalysis, prothrombin time, and activated partial thromboplastin time — are recommended for all patients with CVT^{57,58}. These tests are not helpful to establish the presence of CVT itself, but they can contribute to the identification of associated conditions, such as

anaemia, liver disease, kidney disease and inflammatory or infectious conditions. The results of genetic testing for thrombophilia rarely change management, but this test can be considered for patients who have no CVT risk factors, patients with recurrent thrombosis, patients with a family history of venous thrombosis, or in the setting of warfarin-induced skin necrosis^{25,57,58}. Haemoglobin electrophoresis should be performed in suspected cases of sickle cell disease or thalassaemia. Lumbar puncture should only be performed in special circumstances, for instance when a CNS infection is suspected⁵⁹.

Imaging. Prompt investigation by noninvasive imaging is required when CVT is clinically suspected. Magnetic resonance venography and CT venography are both adequate for diagnosis of CVT, but the former is clearly superior for the visualization of brain parenchymal lesions^{55,58,60} (FIG. 3). Theoretically, catheter angiography remains the most accurate method for diagnosis of CVT but is almost never required anymore. As catheter angiography is an invasive technique with a non-negligible risk of stroke, a patient should only undergo this procedure when CT venography or magnetic resonance venography are inconclusive, a dural arteriovenous fistula is suspected, or when an endovascular therapeutic intervention is planned^{61–66}.

The classic sign of acute CVT on unenhanced CT images is an increased attenuation of the occluded sinus^{67,68}. Depending on the location of the hyperdense vessel, this finding is sometimes termed a ‘dense triangle sign’ (representing a clot in the superior sagittal sinus) or a ‘cord sign’ (representing thrombosis of cortical or deep veins)^{69–71}. Contrast injection can reveal an ‘empty delta sign’, which results from contrast enhancement of the wall of the thrombosed sinus owing to collateral circulation. However, these signs are only present in a limited proportion of patients, are even less common in sub-acute or chronic cases, and are not sufficiently specific for diagnosis of CVT^{60,68,69,72}.

CT venography provides a detailed depiction of the cerebral venous system, and enables correct identification of sinuses in ~99% of patients and cerebral veins in ~88% of patients⁷³. CT venography is also more sensitive to low blood flow than is time-of-flight (TOF) magnetic resonance venography, which tends to overestimate the degree of thrombosis in cases of partial vessel occlusion^{74–76}. However, some anatomic variants can mimic CVT, especially sinus atresia, sinus hypoplasia or sinus filling defects caused by prominent arachnoid granulations. Detection of isolated cortical vein thrombosis can be especially challenging with CT venography^{65,76}. Nevertheless, CT venography is generally a reliable alternative to MRI, particularly in patients with severe CVT in whom MRI is not feasible, or in patients with a contraindication for MRI. Disadvantages of CT venography are exposure to ionizing radiation and the need for contrast material.

Magnetic resonance venography has several limitations when used alone, particularly in patients with a hypoplastic sinus, cortical vein thrombosis or partial sinus occlusion; consequently, a complete MRI study is

Table 1 | Conditions associated with CVT

Risk category	Risk factor	Prevalence in patients with CVT*	Study type
Permanent risk factors			
Hereditary thrombophilia	Hereditary thrombophilia (total)	34–41%	Cohort
	Factor V Leiden thrombophilia	9–13%	Case-control
	Prothrombin Gly20210Ala mutation	9–21%	Case-control
	Antithrombin deficiency	3%	Case-control
	Protein S deficiency	2–3%	Case-control
Systemic diseases	Protein C deficiency	2–5%	Case-control
	Cancer	7%	Cohort
	Myeloproliferative neoplasms	2–3%	Cohort
	Inflammatory bowel disease	2–3%	Cohort
	Behçet disease	1%	Cohort
	Thyroid disease	2%	Case reports
	Systemic lupus erythematosus	1%	Case series
	Antiphospholipid syndrome	6–17%	Cohort
	Nephrotic syndrome	1%	Case reports
	Sarcoidosis	<1%	Case reports
Miscellaneous	Paroxysmal nocturnal hemoglobinuria	NA	Case series
	Dural arteriovenous fistula	2%	Cohort
Miscellaneous	Obesity	23%	Case-control
	Transient risk factors		
Sex-specific	Oral contraceptives	54–71% [†]	Case-control
	Pregnancy and puerperium	11–59% [†]	Cohort
	Hormone replacement therapy	4% [†]	Cohort
Iatrogenic	Lumbar puncture	2%	Cohort
	Neurosurgical operation	1%	Cohort
	Jugular vein catheterization	1%	Cohort
Miscellaneous	Infections of the head or neck	8–11%	Cohort
	Anaemia	9–27%	Case-control
	Head trauma	1–3%	Cohort
	Spontaneous intracranial hypotension	NA	Case reports
	Dehydration	2%	Cohort

*For estimates of the prevalence, we used data from two large cohort studies of patients with cerebral venous thrombosis (CVT) and data from controlled studies that examined that particular risk factor^{11,13}. For each risk factor, we list the type of study on which the association is based. [†]Percentage of women. NA, not available.

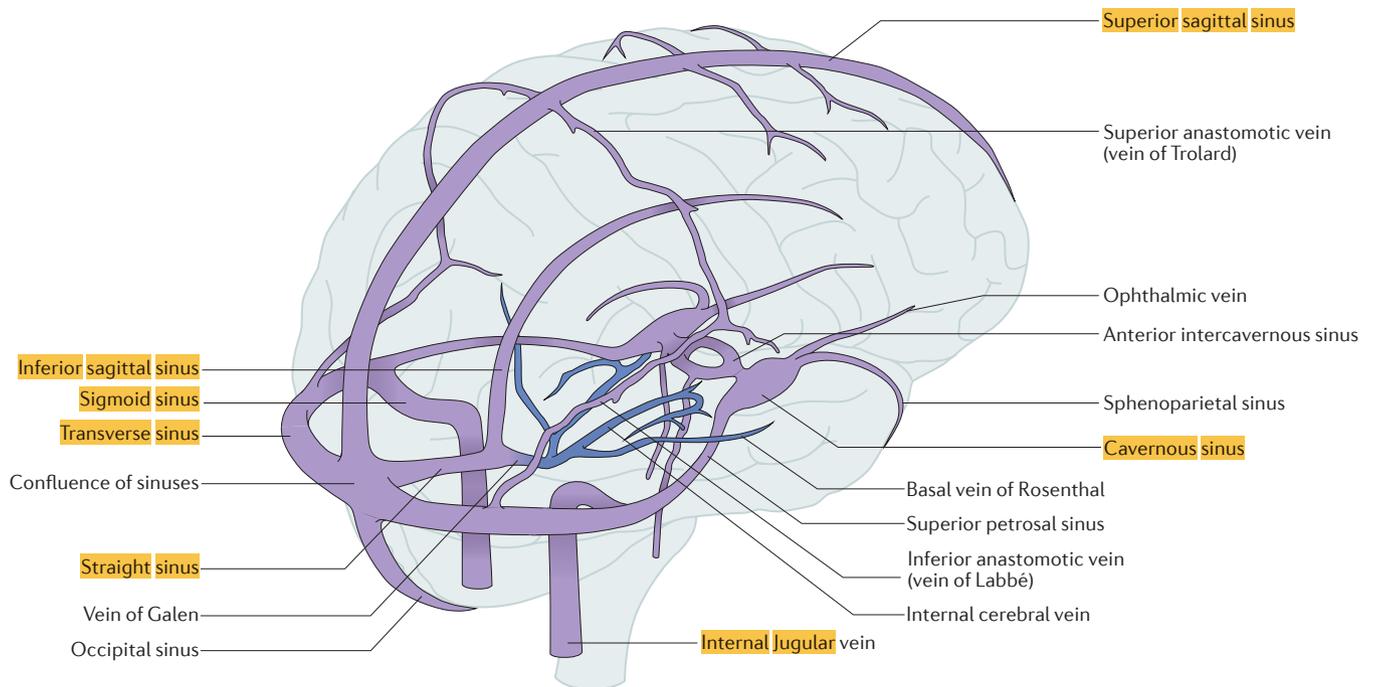


Figure 1 **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

required to enable diagnosis of CVT^{60,77}. When performing MRI, use of T2*-weighted gradient-recalled echo or susceptibility-weighted imaging is recommended so as to maximize diagnostic accuracy, especially in the acute phase of CVT and in patients with suspected isolated cortical vein thrombosis⁶¹. These sequences show intraluminal thrombi as hypointense areas caused by increased levels of deoxyhemoglobin^{65,78–80}. Contrast-enhanced magnetic resonance venography is more sensitive than TOF magnetic resonance venography, particularly for sinuses with a small diameter and/or slow blood flow^{60,81}. Use of 3D T1-weighted black-blood sequences has produced promising results in a single study in patients with subacute CVT⁸².

When parenchymal lesions are present, characteristic patterns should raise suspicion of CVT. For example, **venous infarcts often cross arterial boundaries**. Clear demarcation and **disproportionate space-occupying lesions** observed with CT in the first hours of onset of focal signs also **suggest CVT**^{58,83}. **Haemorrhage** commonly occurs in **combination** with **oedema**, but various patterns might be observed, ranging from scattered subcortical foci to a lobar haematoma. Small juxtacortical haemorrhages were shown to be very specific for thrombosis of the superior sagittal sinus⁴⁰. **Bilateral** parenchymal lesions are found in about **one-third** of patients with CVT and nonhaemorrhagic lesions⁸⁴.

Treatment

General care. A schematic overview of the diagnostic and therapeutic steps in CVT is provided in FIG. 4. Current guidelines recommend that patients with CVT are admitted to a **stroke unit**⁵⁸. Any underlying

condition that might have contributed to the disease should be corrected if possible — especially infection or dehydration⁸⁵. Patients with acute symptomatic seizures should be treated with antiepileptic drugs to prevent recurrent seizures; those with a supratentorial haemorrhagic parenchymal lesion are most at risk of acute symptomatic seizures^{47,48,54,86}. Prophylactic antiepileptic drugs could be an option in these patients, although this approach is not uniformly accepted^{158,87}.

Anticoagulation. **Heparin** was first introduced as a treatment for venous thrombosis in the late 1930s. Stansfield, a British gynaecologist, was one of the first to describe a favourable outcome for a patient with puerperal CVT who was treated with heparin. In his 1942 paper, published in the *British Medical Journal*, Stansfield remarked that “the introduction of heparin gives us an effective weapon to treat what has invariably been a fatal complication of the puerperium, and the clinician’s reward for an early diagnosis will be the survival of the patient rather than the sterile pleasure of making an accurate diagnosis and confirming it in the post-mortem room” (REF. 88). Stansfield’s decision to use heparin was motivated by a previous fatal case of puerperal CVT and encouraging results of heparin treatment in patients with leg-vein thrombosis.

The use of heparin for treatment of CVT became more frequent following publication of Stansfield’s paper, but its use remained controversial for many decades⁸⁹. Those who were opposed to heparin therapy were concerned about the high incidence of ICHs in patients with CVT^{11,13,90}. On the other hand, advocates of anticoagulation argued that withholding heparin could lead

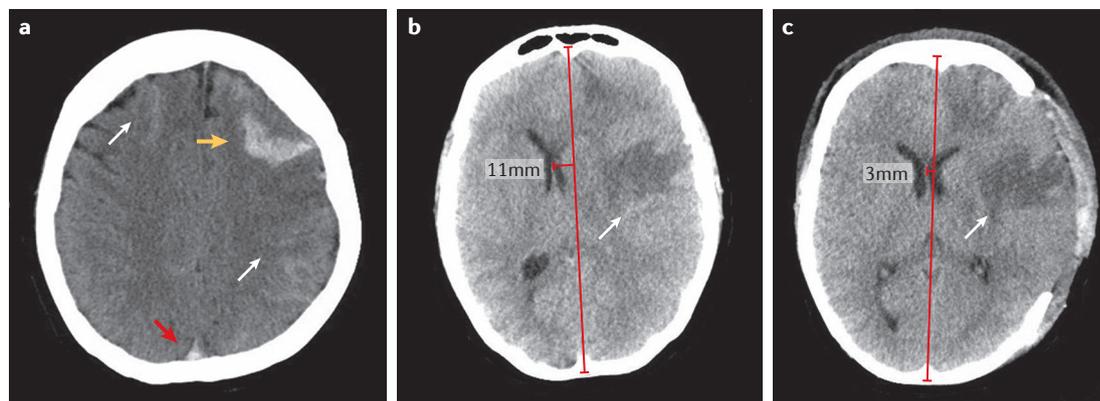


Figure 2 | Imaging findings in a patient with cerebral venous thrombosis. **a** | Axial non-contrast-enhanced CT scan of an intracerebral haemorrhage in the left frontal lobe (yellow arrow) with pericerebral oedema, as well as convexity subarachnoid haemorrhage (white arrows). Note also the hyperdense aspect of the superior sagittal sinus (red arrow). **b** | CT scan of the same patient as in part **a**, taken a few days later, after she had clinically deteriorated and become comatose. CT scan shows progressive left-sided oedema (arrow) and radiological signs of transtentorial herniation with a midline shift of approximately 11 mm. **c** | Postoperative CT scan of the same patient as in parts **a** and **b** after emergency left-sided decompressive hemicraniectomy was performed, showing a reduction in mass effect, as evidenced by the decrease in midline shift.

to growth of the thrombus, causing new venous infarcts and haemorrhages⁹¹. In a disease as rare as CVT, clinical trials to solve this dilemma were a challenge. Nonetheless, in the 1990s, two small randomized trials were conducted. A meta-analysis of these trials, which included a total of 79 patients, showed a nonsignificant difference in clinical outcome in favour of heparin (relative risk of death 0.33, 95% CI 0.08–1.21)^{92–94}. Importantly, no new ICHs occurred in patients treated with heparin, whereas two patients in the control group had a new ICH, and two experienced a probable pulmonary embolism. Despite the small number of patients and statistical uncertainty, these trials convinced most experts that heparin is beneficial for patients with CVT. Guidelines from both the European Federation of Neurological Societies and the American Heart Association now recommend anticoagulation with a therapeutic dose of heparin as the primary treatment for CVT, regardless of whether patients have an ICH at baseline^{58,87}.

No consensus exists as to whether unfractionated heparin (UFH) or LMWH should be used for the treatment of CVT. In patients with leg-vein thrombosis and pulmonary embolism, LMWH is associated with a lower risk of major bleeding, thrombotic complications, and death than that associated with UFH⁹⁵. A nonrandomized comparison between LMWH and UFH suggests that in CVT, LMWH also leads to better outcomes⁹⁶. This observation has been confirmed by a single-centre randomized trial, whereas another small trial found no difference in clinical outcome^{97,98}. The results of both trials must be interpreted with caution, owing to their low methodological quality. Surprisingly, despite the rather compelling evidence that LMWH is superior to UFH for the treatment of CVT, surveys indicate that many physicians — especially neurologists — still prefer UFH^{99,100}.

For patients with CVT who are medically stable, treatment with a vitamin K antagonist should be initiated. The duration of treatment is generally between 3

and 12 months, or longer in rare cases^{58,87}. The optimal duration of anticoagulant treatment is not known and is currently being evaluated in the extending oral anticoagulant treatment after cerebral vein and dural sinus thrombosis (EXCOA-CVT) study¹⁰¹. The question of whether patients with CVT can be safely treated with direct oral anticoagulants (DOACs) has not yet been answered^{102,103}. In patients with leg-vein thrombosis or atrial fibrillation, DOACs exhibit a similar efficacy as heparin followed by vitamin K antagonists, but are associated with a substantial reduction in the risk of ICH. The perception that DOACs have a superior safety profile to that of conventional anticoagulants make them attractive candidate drugs for the treatment of CVT^{104–106}, and a phase III trial evaluating the efficacy and safety of the DOAC dabigatran in patients with CVT is currently recruiting participants¹⁰⁷.

Endovascular treatment. Endovascular treatment for CVT was first reported in the late 1980s^{108,109}. In the past two decades, countless case reports and small case series have been published, but no randomized trials^{110,111,112}. The success of endovascular treatment for acute ischaemic stroke has fuelled further enthusiasm for use of this therapy in CVT; however, importantly, the transvenous approach that is generally used in patients with CVT is very different from the endovascular techniques used in acute ischaemic stroke, despite the fact that the same thrombectomy devices are sometimes used. Broadly speaking, two distinct approaches can be used for the endovascular treatment of CVT. One is chemical thrombolysis, in which a microcatheter is advanced through the thrombus, and a thrombolytic drug — usually urokinase or recombinant tissue plasminogen activator — is infused locally^{112,113}. The other is mechanical thrombectomy with, for instance, a rheolytic device, balloon angioplasty or a stent retriever. A combination of both techniques is

Box 1 | Presenting symptoms and signs in CVT

- Headache: 70–90%
- Seizure: 30–40%
- Papilloedema: 30–60%
- Focal motor deficits: 30–50%
- Aphasia: 15–20%
- Mental status disorder: 15–25%
- Coma: 5–15%
- Movement disorder: rare

Data derived from three large cohort studies^{11,12,45}.

sometimes applied. Judging by the number of publications, mechanical thrombectomy is increasingly being used, perhaps because interventionalists have gained more experience with use of these techniques in ischaemic stroke^{112,114–116}. Recanalization (partial or complete) is reported in ~70–90% of patients; however, owing to a lack of agreement on how to score recanalization in CVT, these percentages have limited value. Reliable data on the risk of complications are also not available, but systematic reviews of case series estimate a frequency of postprocedural new ICHs of 10–17%^{64,110,116}. The safety and efficacy of endovascular treatment have been assessed in the thrombolysis or anticoagulation for cerebral venous thrombosis (TO-ACT) trial. This trial was terminated prematurely because of futility. The first results were presented at the 2017 European Stroke Organization Conference. In total, 67 patients with severe CVT were randomly assigned to receive endovascular (65%) or standard (66%) treatment, and no difference was observed in the proportion of patients with a good clinical outcome at 12 months follow-up. The full results of the TO-ACT trial are currently awaited, but on the basis of the available information, endovascular treatment should not be routinely applied in patients with CVT¹¹⁷.

Complications

Hydrocephalus. Some degree of hydrocephalus occurs in ~15% of patients with CVT^{14,118}. Most of these patients have obstructive hydrocephalus owing to oedema of the basal ganglia and thalami, which results from thrombosis of the deep venous system. Hydrocephalus increases the risk of a poor clinical outcome, but whether the increase in risk is due to the hydrocephalus or to the underlying parenchymal damage is unclear. This uncertainty and the fact that patients require anticoagulation means that a shunting procedure should only be considered in critically affected patients, in whom no condition other than the hydrocephalus can explain their clinical situation^{118,119}.

Intracranial hypertension. Intracranial hypertension is very common in the acute phase of CVT. In most patients, symptoms are limited to headache with or without papilloedema, in which case treatment can be confined to anticoagulation and analgesics. Acetazolamide can reduce intracranial pressure to some

extent by lowering cerebrospinal fluid production, but its effect is insufficient to have a substantial positive influence in the acute phase of CVT. The use of steroids has been evaluated in a post-hoc analysis of the International Study on Cerebral Vein and Dural Sinus Thrombosis. In this study, steroids were not associated with an improved outcome. In fact, in patients without parenchymal lesions, steroids appeared to be detrimental. As a result, steroids are not recommended for the treatment of CVT^{58,87,120}.

Infrequently, patients can develop decreased visual acuity as a result of intracranial hypertension; in these individuals, especially in those with acutely threatened vision, immediate reduction of pressure by a lumbar puncture or neurosurgical shunting procedure is indicated^{58,87,91}. In a subset of patients, intracranial hypertension causes a decrease in consciousness, sometimes even coma, in the absence of focal parenchymal lesions. These patients are believed to have severe intracranial hypertension, resulting in decreased cerebral perfusion. Evidence-based treatment recommendations cannot be provided for such cases, as almost no literature exists on this topic. In rare cases, these patients have been treated with an emergency shunting procedure or bilateral decompressive hemicraniectomy¹¹⁹.

Transtentorial herniation. The main cause of early death in patients with CVT is transtentorial herniation owing to mass effect from a parenchymal lesion¹²¹. In patients with clinical and radiological signs of impending herniation, decompressive surgery should be performed⁸⁷. A number of studies have shown that the outcome of patients with CVT and impending herniation who undergo decompressive surgery is often favourable^{122–126}. Although these studies were uncontrolled, we know from previous studies that without decompressive surgery, most of these patients will succumb to the disease¹²⁷.

Prognosis

The clinical course of CVT is unpredictable in the first days after diagnosis, and about one quarter of patients deteriorate in that phase¹¹. Despite the sometimes grim outlook in the acute phase, multicentre cohort studies have taught us that the long-term outcome of most patients with CVT is favourable¹¹. Death in the acute phase occurs in ~4% of patients and, as mentioned previously, is generally due to transtentorial herniation^{11,121,128}. Status epilepticus and medical complications such as sepsis and pulmonary embolism are other possible causes of early death in patients with CVT¹²¹. The long-term risk of death is ~8–10%, and about half of these deaths result from an underlying condition, most often cancer^{11,128}. A substantial decrease in mortality in patients with CVT has been observed over the past few decades¹²⁹. Although improvement of care and a shift in risk factors might partly account for this change, the most important contributing factors are probably an increased awareness of CVT among clinicians, and improved imaging techniques, which have led to earlier diagnosis and detection of less-severe cases.

About 6–10% of surviving patients with CVT have severe and permanent disability¹¹. Predictors of poor outcome include older age, male sex, coma, mental status disorder, ICH, thrombosis of the deep venous system, infection of the CNS, cancer, and hyperglycaemia at admission^{11,130,131}. However, an infection outside of the CNS is not associated with a poor outcome in

patients with CVT²⁸. Excellent outcomes can generally be expected for patients who present with isolated intracranial hypertension^{11,132}. On the other hand, mortality of >30% has been reported in series of patients with severe CVT admitted to an intensive care unit^{133,134}.

Despite the fact that ~80% of patients recover from CVT without physical disability, many of these patients do experience residual chronic symptoms. About half of patients report headache during follow-up, and severe headaches that require bed rest or hospital admission persist in 14% of patients^{11,135}. More than half of survivors of CVT report subtle neuropsychological difficulties or depression. These complaints are often associated with a negative effect on employment status: ~20–40% of patients are unable to return to their prior working life^{135–138}. In one study, a low level of education was associated with an increased risk of unemployment after CVT¹³⁶.

Remote seizures occur in ~10% of patients after CVT, a far lower proportion than that seen in the acute phase of CVT. Remote seizures are more likely to occur in patients with early seizures, motor deficits, and supratentorial lesions — especially if haemorrhagic^{47,136}. Severe visual loss due to intracranial hypertension is rare, but ophthalmological evaluation should be performed in patients with papilloedema or visual complaints¹³⁹.

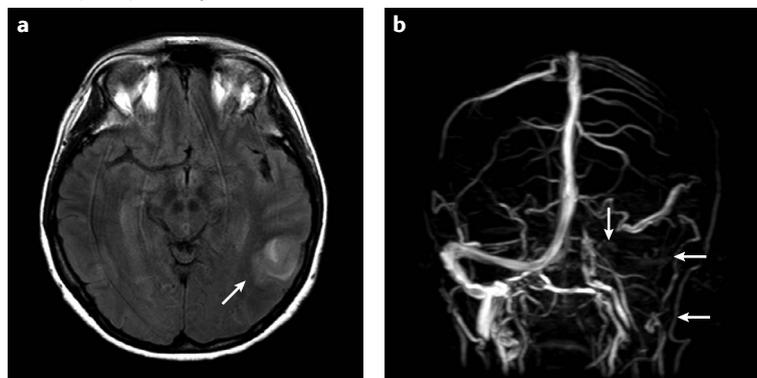
Recanalization

The rate of spontaneous venous recanalization in patients with CVT is ~85%¹²⁸. Analysis of the time to recanalization indicates that this process predominantly occurs in the first few months after CVT, but that it can take up to 1 year^{140–142}. Studies of the relationship between recanalization and clinical outcome have produced conflicting results^{128,140,141,143}. Most of these studies have only examined an association between disability (measured by the modified Rankin scale) and recanalization, so data regarding the association of recanalization with other long-term complaints are scarce. Persistent intracranial hypertension or chronic headache after CVT might indicate the existence of a post-thrombotic syndrome, similar to that seen in some patients with leg-vein thrombosis¹⁴¹. Whether persistent occlusion increases the risk of CVT recurrence also remains a poorly addressed issue. Such an association has been shown in paediatric patients but comparable data for adults are not available^{141,144}. Despite the scant data on recanalization and clinical outcome, documentation of the extent of recanalization with follow-up imaging can be useful in clinical practice as it facilitates diagnostic work-up in patients for whom recurrence of CVT is suspected. Without routine follow-up imaging, determining whether thrombosis has recurred when a patient experiences a new-onset headache after CVT is often very difficult²⁸.

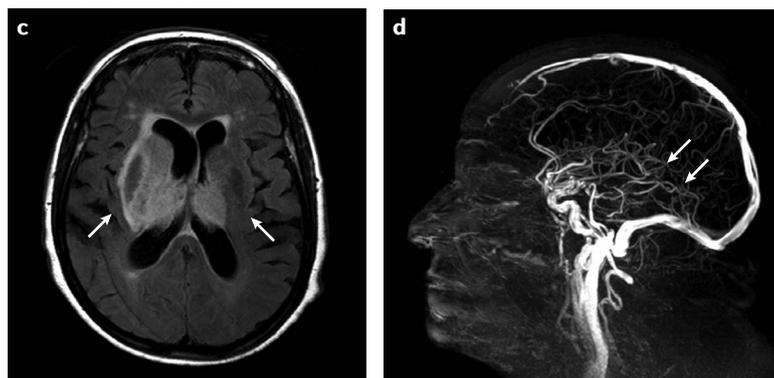
Recurrence and long-term management

The risk of a new cerebral or systemic venous thrombotic event after an episode of CVT is ~4 per 100 person-years, and most recurrences are within the first year¹⁴⁵. Male sex and polycythaemia or thrombocythaemia are established risk factors for recurrence^{145,146}. Severe

Left temporal parenchymal lesion



Bilateral thalamic oedema



Juxtacortical haemorrhage

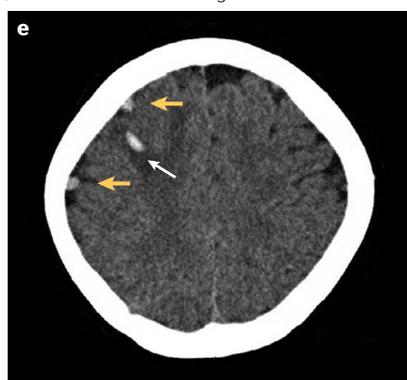


Figure 3 | Illustrative brain parenchymal lesions in patients with cerebral venous thrombosis. **a** | Fluid attenuation inversion recovery (FLAIR) shows a left temporal parenchymal lesion (arrow) in a patient with thrombosis of the left lateral sinus and jugular vein. **b** | Magnetic resonance venography in the same patient as in part **a** shows an absence of flow in the left lateral sinus and jugular vein (arrows). **c** | FLAIR shows bilateral oedema of the thalami and basal ganglia in a patient with thrombosis of the deep venous system (arrows). **d** | Magnetic resonance venography in the same patient as in part **c** shows no visible filling of the deep venous system (arrows). **e** | Axial noncontrast-enhanced CT scan of a small juxtacortical haemorrhage with surrounding oedema (white arrow) in a patient with superior sagittal thrombosis and cortical vein thrombosis. Note the hyperdense cortical veins, indicating thrombosis (yellow arrows).

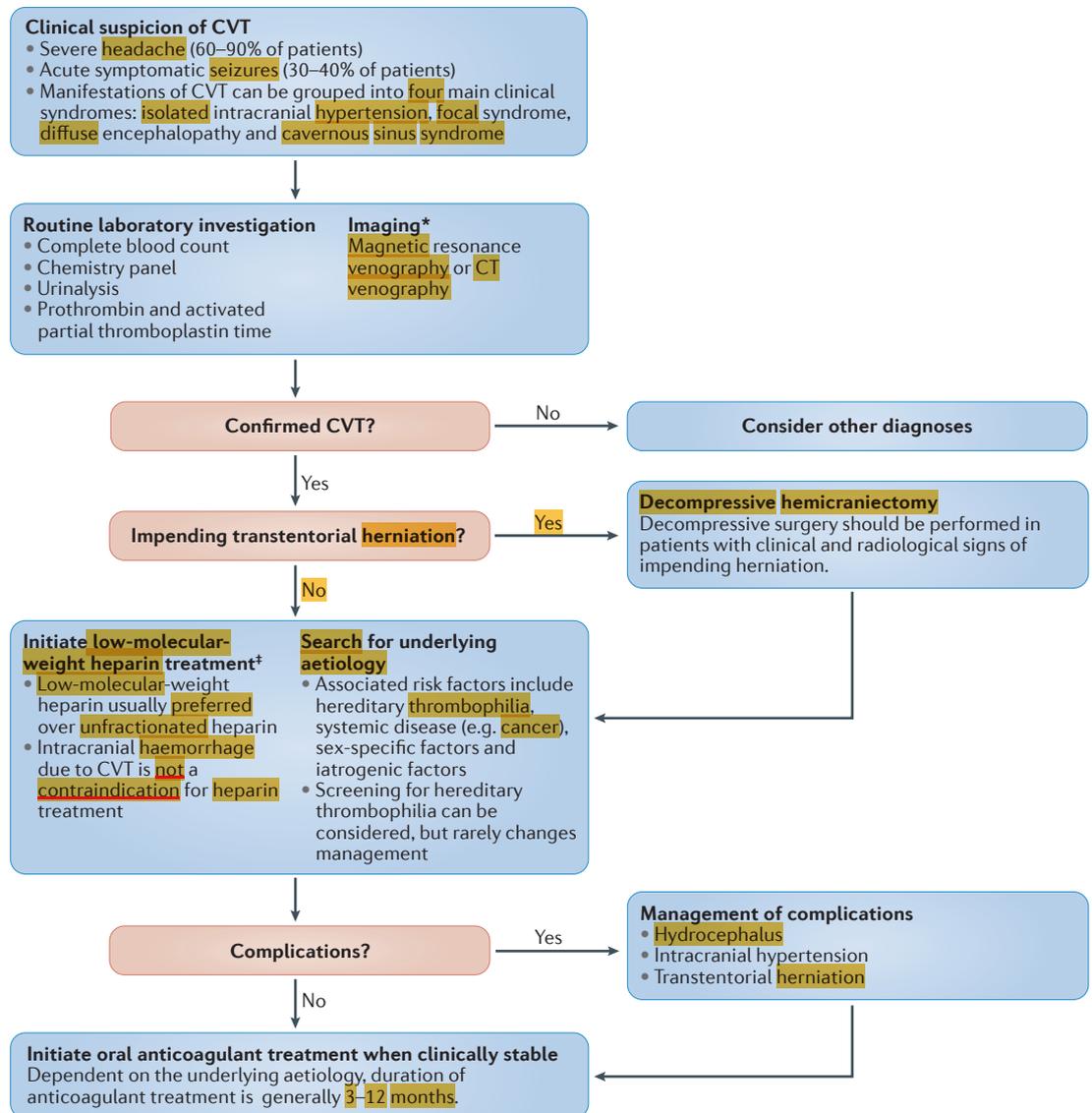


Figure 4 | Schematic overview of diagnostic and therapeutic steps in CVT. *MRI is the most suitable modality for detecting brain parenchymal lesions; magnetic resonance venography and CT venography are equally adequate for diagnosis of cerebral venous thrombosis (CVT), but magnetic resonance venography is superior for detecting cortical vein thrombosis and establishing the age of the thrombus; CT venography is sufficient in the acute phase in patients who are severely affected or have a contraindication for MRI. †The use of low-molecular-weight heparin is generally preferred over unfractionated heparin, except when the need for rapid reversal of anticoagulation is anticipated, for instance because of emergency neurosurgical intervention.

thrombophilia and previous noncerebral venous thromboembolism have also been associated with an increased risk of recurrence in some cohorts^{13,147}. However, results regarding the association between recurrence and duration of anticoagulation are conflicting^{13,145,147}, and a trial comparing short-term (3–6 months) with long-term (12 months) anticoagulation is currently ongoing¹⁰¹.

Oestrogen-containing contraception and hormonal therapy increase the risk of thrombosis and, consequently, women should be advised not to use these drugs after CVT. Although pregnancy is associated with an increased risk of venous thrombotic events, the absolute risk of recurrent events related to subsequent pregnancy among women who have a history of CVT

is low: estimated rates are nine cases of CVT and 27 of noncerebral venous thromboembolism per 1,000 pregnancies^{11,58,148,149}. A history of CVT, therefore, should not be a contraindication for future pregnancies, but women of child-bearing age should be informed of the increased relative risk of pregnancy-related thrombotic events and the possible benefit of antithrombotic prophylaxis¹⁴⁹.

Future research directions

Burning clinical issues that remain to be addressed include the efficacy and safety of endovascular treatment, the optimal duration of anticoagulant treatment, and whether DOACs can be safely applied in these patients. The TO-ACT, EXCOA-CVT and RE-SPECT

CVT trials, respectively, are currently addressing these three issues, and results are expected in the next few years^{101,107,117}. The prospective DECOMPRESS-2 registry, in which CVT patients who undergo decompressive surgery are included, will provide an improved forecast of the clinical outcome in these patients. An increased understanding of the risk factors that are associated with CVT, both genetic and acquired, is also required. Efforts have been made to form an international collaboration to identify new genes and biomarkers associated with CVT¹⁵⁰.

Conclusions

In the past few years, we have seen major advancements in our knowledge of the epidemiology, diagnosis and treatment of CVT. Once considered to be an invariably fatal condition, CVT is now viewed as a disease with a generally favourable prognosis. Although more common than previously believed, CVT is still a fairly infrequent disease. As a result, our only hope to gain further insights into the genetics, associated conditions and treatment of this multifaceted condition is through international collaborations.

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Author contributions

S.M.S. and D.A.d.S. researched the data for the article and co-wrote the first draft. J.M.F. and J.M.C. made substantial contribution to discussion of the context and edited the manuscript before submission. J.M.C. supervised the preparation of the manuscript.

Competing interests statement

J.M.F. has received personal fees from Boehringer Ingelheim and Daiichi Sankyo. J.M.C. has received research grants for CVT from two non-profit organizations: the Dutch Thrombosis Society and the Netherlands Brain Foundation, and is a steering committee member of the RE-SPECT CVT trial, a clinical trial that evaluates the efficacy and safety of dabigatran for the treatment of CVT sponsored by Boehringer Ingelheim.

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