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INVITED REVIEW

Cerebral venous thrombosis

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Summary. Cerebral venous thrombosis (CVT) is an uncommon cause of stroke that mainly affects young adults and children. In contrast to venous thromboembolism, women are affected three times more often than men. Baseline symptoms can vary considerably between patients, but most present with headache, seizures, or focal neurological deficits. Patients can be diagnosed with magnetic resonance imaging, computerized tomography-venography, or catheter angiography, although the latter is rarely required anymore. Approximately 30–50% of patients have an intracerebral hemorrhage, which can range from a small juxtacortical hemorrhage to large space-occupying lesions. Based on limited evidence from clinical trials, the primary therapy for CVT is anticoagulation with heparin. Uncontrolled studies have shown promising results for the use of endovascular treatment in severely affected patients, but these studies require confirmation in prospective clinical trials. In patients who develop clinical and radiological signs of impending herniation decompressive surgery can be both life saving and result in a good functional outcome.

Keywords: cerebral thrombosis; decompressive craniectomy; hemorrhage; heparin; sinus thrombosis; stroke.

Introduction

The cerebral veins are an unusual site of thrombosis, and cerebral venous thrombosis (CVT) is a distinct cause of stroke. In contrast to both venous thromboembolism (VTE) and arterial stroke, CVT predominantly affects young adults and children. Patients can present with a range of signs and symptoms. Due to this variability in clinical manifestations, and the rarity of the condition, CVT can be difficult to diagnose. In this review, I will give an overview of the epidemiology, diagnosis, and treatment of CVT in adults.

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Historical perspective

The first description of CVT is attributed to the French physician Ribes, who, in 1825, described a patient with severe headache and epilepsy due to thrombosis of the superior sagittal and lateral sinuses [1,2]. The first case of puerperal CVT dates back to 1828, when John Abercrombie, physician to King George IV of England, published a detailed report of a 24-year-old woman who developed headaches and seizures 2 weeks after an otherwise unremarkable delivery. She died of a status epilepticus (despite treatment with repeated bloodletting). At post-mortal examination, Abercrombie identified a thrombosis of the superior sagittal sinus and cortical veins [3]. Larger single-center studies were published in the second half of the 20th century, which provided a broader insight into the variable clinical manifestations and risk factors associated with CVT [1,4]. Multi-center studies with data of more than 100 patients have been published in the last 25 years, the largest of which are the 'international study on cerebral vein and dural sinus thrombosis' (ISCVT, 624 patients) and an Italian (706 patients) registry [5,6].

Epidemiology

The first calculations of the incidence of CVT were extrapolated from autopsy series and provided estimates of 0.1–0.2 cases per 100 000 [7]. A recent population-based study found a 5- to 10-fold higher incidence among adults (1.3 per 100 000) [8]. In developing countries, the incidence is probably even higher [9]. The increase in incidence is most likely explained by the improvement in imaging techniques, which enabled identification of less severe cases. The higher incidence rates also suggest that, unlike previously believed, CVT may be more common in adults than in children, although direct comparisons have not been performed [10].

Risk factors

Most adult patients with CVT are between the ages of 20 and 50, and < 10% are older than 65 [11]. In young and

middle-aged adults – but not in children or elderly – CVT is three times more common among women than men. This skewed sex ratio is the result of gender-specific risk factors: oral contraceptives, pregnancy or (more frequently) puerperium, and hormonal replacement therapy [12]. Interestingly, these factors are also associated with VTE, but in this condition, the sex ratio is evenly distributed [13]. A possible explanation is that men intrinsically have a higher risk of VTE, as supported by the observation that, compared to women without reproductive risk factors, VTE is twice as common in men [14]. In contrast, if the same type of analysis is performed in patients with CVT, the sex ratio is 1 : 1 [12].

Many other risk factors have been associated with CVT, and an overview is provided in Table 1. One should bear in mind that this list is not complete and that the level of certainty of the association varies per risk factor. Some, like sarcoidosis, have only been reported in case reports, and the presumed relationship could be coincidental, or due to a confounding variable, like steroid treatment. Most of the risk factors for CVT coincide with those for VTE, such as genetic thrombophilia, antiphospholipid syndrome, inflammatory bowel disease, and malignancies [5,15]. Risk factors specific for CVT are local conditions of the head and neck, such as head trauma, neurosurgical interventions, and regional infections. Although the absolute number of patients is low, acute lymphoblastic leukemia is infamous for being associated with CVT, most likely related to asparaginase therapy [16].

Prognosis

The mortality of CVT has decreased steadily over the last decades and is currently between 5% and 10% [17]. The most important explanation for this decline is the same as the reason for the increase in incidence: the identification of less severe cases. Early mortality is usually caused by transtentorial cerebral herniation due to large space-occupying lesions or generalized cerebral edema [18]. Delayed death is more frequently caused by an underlying condition – especially cancer – or recurrent thrombotic events. Approximately 80% of patients recover without functional disability, although many do suffer from chronic symptoms such as headache, fatigue, and concentration difficulties, which often negatively impact their life [5,6,19]. Based on baseline variables that are associated with poor outcome, a risk score has been developed which can be used to predict clinical outcome at follow-up [20]. Estimates of the risk of a recurrent thrombotic event vary between 0% and 10%, although the number of adequately sized cohort studies with a long follow-up is small [6,21].

Table 1 Causes and risk factors for cerebral venous thrombosis

Genetic thrombophilia	**Systemic diseases**
Gender-specific risk factors	Cancer (especially hematological malignancies)
Oral contraceptives	Inflammatory bowel disease
Pregnancy/puerperium	Thyroid disease
Hormone replacement therapy	(Neuro)sarcoidosis
Infections	Behçet disease
Meningitis	Systemic lupus erythematosus
Otitis/mastoiditis	Antiphospholipid syndrome
Systemic	**Miscellaneous causes**
Iatrogenic causes	Dural arteriovenous fistula
Intracranial hypotension after lumbar puncture	Arteriovenous malformation
Neurosurgical operation	Head trauma
Catheterization jugular vein	Dehydration
Medications (e.g. asparaginase and steroids)	Anemia
	Spontaneous intracranial hypotension

Pathophysiology

To explain the symptomatology of CVT, it is helpful to distinguish two separate pathophysiological mechanisms: thrombosis of the major cerebral sinuses and thrombosis of the cortical veins. The cerebral sinuses, besides draining blood, are essential for the transportation of cerebrospinal fluid, a process mediated by the arachnoid villi, which are also known by their eponym *Pacchioni's granulations* [22]. These villi are small protrusions of the arachnoid mater into the cerebral sinuses and facilitate transport of cerebrospinal fluid from the subarachnoid space to the blood. Occlusion of the cerebral sinuses blocks transport of cerebrospinal fluid, which results in intracranial hypertension. The second mechanism, occlusion of a cortical vein, obstructs the drainage of blood from the adjacent brain tissue. Depending on the extent of the thrombus and the availability of venous collaterals, occlusion of a cortical vein causes an increase in venous and capillary pressure and breakdown of the blood–brain barrier [23]. This process can result brain tissue damage, which is described in more detail below.

Clinical manifestations and diagnosis

Headache is the most common presenting symptom of CVT and the intensity is usually severe. In a subset of patients, the onset of headache is acute, similar to a subarachnoid hemorrhage. A minority of patients (10%) do not report headache at baseline. The absence of headache is more common in men, elderly, patients with cancer, and in isolated cortical vein thrombosis [24]. Seizures and focal neurological deficits, such as hemiparesis and aphasia, can occur in the presence of a brain parenchymal lesion. Approximately 40% of patients suffer from one or more seizures in the acute phase, which is much higher than in arterial stroke. While any combination of signs and symptoms is possible, most patients with CVT present with one of the following clinical syndromes: isolated intracranial hypertension (headache, decreased visual acuity, and papilledema), focal symptoms (deficits or

seizures), a diffuse encephalopathy, or a cavernous sinus syndrome.

There are three imaging techniques to diagnose CVT: magnetic resonance imaging (MRI) with MR-venography, computerized tomography (CT)-venography and catheter angiography [25]. MRI is the most widely used technique and diagnosis requires visualization of the thrombus within the vessel in combination with absent flow on MR-venography (Fig. 1A,B). Depending on the age of the thrombus, the MRI signal can vary on different sequences [26]. Susceptibility weighted sequences are particularly useful to demonstrate a thrombus within a cortical vein [27]. For MR-venography time-of-flight sequences are most often used although contrast enhanced MR-venography allows better depiction of the venous system [28]. CT-venography is a decent and less expensive alternative to MRI for the diagnosis of CVT, but it is inferior for the visualization of brain parenchymal lesions [29]. Unenhanced CT is generally insufficient for the diagnosis, although a recent small study reported promising results on the diagnostic accuracy of CT density measurement of the dural sinuses in acute CVT [30].

Besides the absence of flow in the cerebral venous system, a variety of lesions of the brain parenchyma can be seen on imaging. Most common is an intracerebral hemorrhage (ICH), which is found in about 30–50% of all

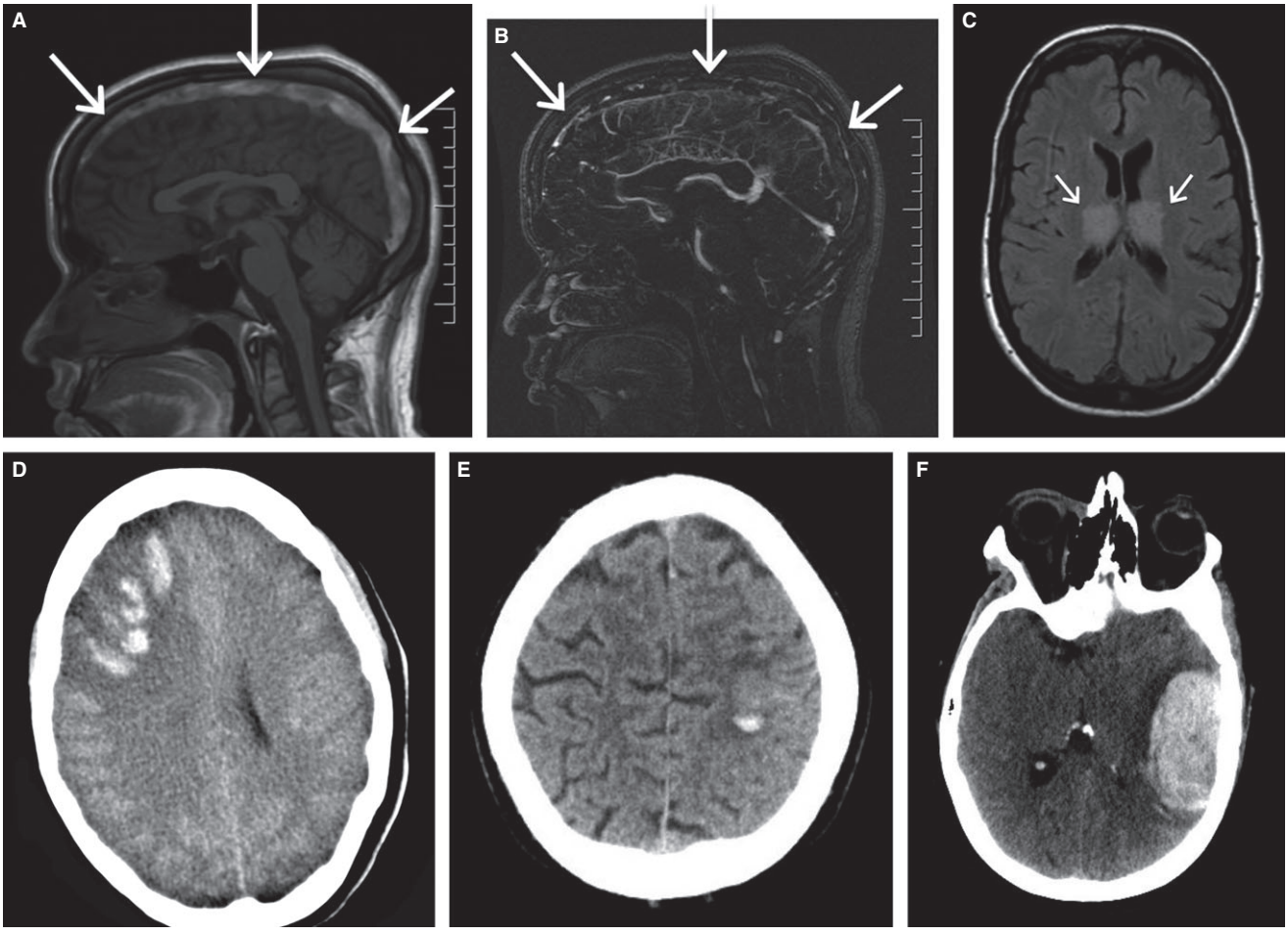

Fig. 1. Imaging findings in patients with cerebral venous thrombosis (CVT). (A, B) Magnetic resonance imaging (MRI) of a 20-year-old male with thrombosis of the superior sagittal sinus. The sagittal T1 sequence (A) shows a hyperintense signal in the superior sagittal sinus, due to methemoglobin in the thrombus (arrows). On the corresponding contrast enhanced MR-venography (B), there is no filling visible of the superior sagittal sinus (arrows). (C) Axial MRI (fluid-attenuated inversion recovery [FLAIR] sequence) of a 43-year-old patient with thrombosis of the deep venous system. A hyperintense signal is present in both thalami (arrows) indicating edema. Clinically, the patient had a mildly decreased consciousness (E4M6V4). (D) Axial non-contrast enhanced computerized tomography (CT) scan of a patient with CVT showing a parenchymal lesion in the right hemisphere. Within the large hypodense area (dark; edema), patchy hyperdense (white) areas are visible, which are hemorrhages. Such lesions are generally termed venous hemorrhagic infarct. (E) Small juxtacortical hemorrhage (JCH) in the left hemisphere of a patient with CVT. Note how the hemorrhage is located just below the cortex and how it follows its curvature. There also is a small amount of edema (darker areas) surrounding the hemorrhage, although this can be hard to visualize on CT. These JCHs are almost exclusively seen in patients with thrombosis of the superior sagittal sinus. (F) Large intracerebral hemorrhage (ICH) in the left temporal lobe in a 52-year-old patient. She had a global aphasia and a right-sided hemiparesis. This patient had an occlusion of Labbé's vein. Sometimes, these ICHs are mistaken for an arterial bleed.

patients [5,26,31]. Localized cerebral edema in the absence of ICH can also be present, especially in the basal ganglia and thalami if the deep venous system is occluded (Fig. 1C). The thrombus within the veins can often be seen on an unenhanced CT scan in these patients, in which case the diagnosis is almost certain. Less common findings are subdural and subarachnoid hemorrhages.

The appearance of ICHs in patients with CVT is highly variable. Most common is an area of brain edema with patchy areas of hemorrhage in it (Fig. 1D). Such a lesion is usually termed 'venous hemorrhagic infarct', although pathologically, this is not an adequate descriptive term, as the edema is often reversible [26]. A distinctive type of ICH in patients with CVT is a juxtacortical hemorrhage. These are small hemorrhages with little or no surrounding edema, localized at the junction between the superficial and deep venous drainage system (Fig. 1E). Juxtacortical hemorrhages are very specific for CVT and almost exclusively occur if the superior sagittal sinus is occluded [31]. Occlusion of Labbé's vein may cause a large ICH of the temporal lobe, which can sometimes be confused with an aneurysmal or other arterial hemorrhage (Fig. 1F).

Routine blood studies including a chemistry panel, complete blood count and prothrombin time, and activated partial thromboplastin time should be performed in all patients with CVT. D-dimer measurements are not used frequently in the diagnostic work-up of patients with suspected CVT. Several studies have examined the sensitivity of D-dimer in CVT and a recent meta-analysis calculated a mean sensitivity of 94% [32]. Among patients with a chronic onset or isolated headache, however, the sensitivity is much lower (83% and 82%, respectively). As these are precisely the type of patients where D-dimer values would be helpful – as there may be no other reason to perform brain imaging in these patients – the value of measuring D-dimers for excluding CVT is limited. Screening for thrombophilia is often performed, although the results rarely change the management of patients [15].

Treatment

Anticoagulation

Heparin is the mainstay therapy for CVT and is recommended by international guidelines [25,33]. This recommendation is based on the data of two small randomized trials [34,35]. Patients treated with heparin had a better clinical outcome, although the difference was not statistically significant in a meta-analysis (relative risk of death 0.33, 95% CI 0.08–1.21) [36]. Importantly, however, heparin was not associated with hemorrhagic complications, which was the main concern of opponents to anticoagulation. In addition, pulmonary emboli, which used to be an important cause of death in patients with CVT prior to the introduction of anticoagulation [37], did not occur in any patient treated with heparin, while two patients in the placebo groups had a diagnosis of probable pulmonary embolism, one of which was fatal. Because of a better safety profile, low molecular weight heparin is generally preferable over unfractionated heparin, except in patients where it is anticipated that rapid reversal of anticoagulation may be required, for instance because of a neurosurgical intervention [38,39].

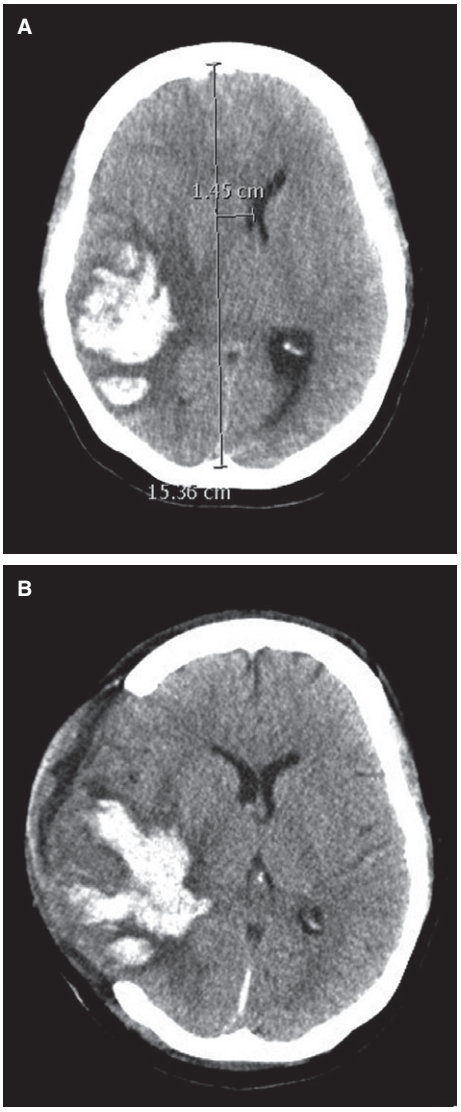

Fig. 2. Decompressive surgery (DS). (A) Preoperative axial computerized tomography (CT) scan showing a large venous hemorrhagic infarct in the right hemisphere of a patient with cerebral venous thrombosis (CVT). There is significant mass effect and a midline shift of approximately 1.5 cm. The patient was comatose (E1M5V2) and had a dilated and fixed pupil on the right side. (B) Postoperative CT scan of the same patient as in (A). After DS, there is a reduction in mass effect and almost normalization of the midline shift. Clinically, the patient also improved. After 12 months follow-up, she had a residual mild hemiparesis and hemianopia.

Endovascular treatment

Endovascular treatment (ET) for CVT was first reported in the 1980s [40]. Since then, a myriad of case reports and small case series have described this approach, but no randomized trials or large prospective studies. The two methods of ET for patients with CVT are intrasinus thrombolysis and mechanical thrombectomy. Judging from the number of publications, thrombectomy appears to gain the overhand in recent years [41], possibly because it is believed to carry a lower risk of hemorrhagic complications. Because of the limited data on its efficacy and potential risk of complications – especially ICHs – ET should not be routinely used in patients with CVT at this stage.

Decompressive surgery

A minority of patients develop large venous hemorrhagic infarcts that result in brain displacement and transtentorial or subfalcine herniation (Fig. 2A). These patients suffer from a decreased consciousness and uni- or bilateral third nerve palsy. Patients can deteriorate very quickly and prompt action is required if there is any hope for survival. During the last two decades, data have amassed which suggest these patients are best treated with decompressive surgery (DS).

During DS, part of the skull on the side of the lesion is temporarily removed to decrease the mass effect and reverse brain displacement (Fig. 2B). In 1999, Stefini *et al*. [42] reported good outcomes after DS in two of three patients with CVT and advanced stages of herniation. Following this article, several studies with similar results have been published [43–45]. All of the evidence for the use of DS in CVT comes from uncontrolled studies. Of course, a randomized trial would offer the highest level of evidence, but most experts believe such a trial is unlikely to be performed. First, only 5–10% of patients with CVT would be eligible for randomization, which makes recruitment of a sufficient number of patients almost impossible. More importantly, one may wonder if a randomized study is even desirable. Transtentorial herniation is the most frequent cause of early death in patients with CVT [18] and the majority of patients with clinical and radiological signs of herniation will die if they are not operated on [45,46]. Compared to this gloomy outlook, the outcome of patients who undergo surgery appears to be so much better that withholding this therapy may be considered unethical.

Conclusion and future directions

Cerebral venous thrombosis is an important cause of stroke in the young. Clinical studies from the past decades have greatly increased our knowledge on how to treat this multifaceted condition and in most patients the prognosis is nowadays favorable. Whether the outcome can be further improved will hopefully be revealed by future research. Three aspects of treatment of CVT are currently being examined in international studies. The TO-ACT trial is a randomized trial in which the efficacy and safety of ET for CVT is being assessed [47]. At the time, this manuscript was written, 51 of the required 164 patients had been included. The DECOMPRESS-2 study is an ongoing prospective registry of consecutive patients who undergo DS and will provide a more robust estimate of the outcome of these patients. Finally, EXCOA is a cluster-randomized trial of short- vs. long-term treatment with oral anticoagulation after CVT. This study was launched recently and the aim was to recruit 900 patients in the coming years. Efforts are also underway to identify new genes and biomarkers that are associated with CVT and which may aid in the diagnosis [48].

One topic that will most likely be examined in the near future is the role of new oral anticoagulants (NOACs) in the treatment of CVT. In patients with VTE and atrial fibrillation, NOACs are associated with an approximate 50% relative risk reduction in ICHs compared to warfarin [49,50]. This observation makes NOACs an attractive candidate drug for the treatment of CVT. With the exception of two small case series, however, no studies have examined the efficacy and safety of NOACs for CVT [51,52]. If a randomized trial is undertaken, one thing is for sure: given the rarity of CVT, it will only succeed through collaboration of large number of hospitals.

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