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Cerebral Venous Thrombosis: A Clinical Overview

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Abstract

Cerebral venous thrombosis (CVT) is a less common cause of stroke that is an often under recognized entity in clinical practice. The goal of this chapter will be to provide clinicians with the knowledge to succinctly recognize the various presentations of CVT, emphasizing rapid diagnosis and the potential treatments necessary to produce optimal clinical outcomes. Detailed descriptions of the relevant anatomy and associated clinical syndromes will be discussed. Detailed sections regarding CVT epidemiology, pathophysiology, etiology, diagnosis and treatment will be provided. Prognosis and long-term follow-up will also be discussed. Relevant literature will be cited and clinical trials across the spectrum of CVT will be highlighted.

Keywords: cerebral venous thrombosis (CVT), etiology, diagnosis, treatment

1. Introduction

Cerebral venous thrombosis (CVT) is a less common cause of stroke that is often under recognized in clinical practice. CVT accounts for 0.5–1% of strokes that has a preponderance to occur in women [1, 2]. The goal of this chapter is to provide clinicians with the knowledge and ability to recognize and treat CVT early in its time course leading to the best clinical outcomes.

2. Anatomy and associated clinical syndromes

The cerebral venous system is a network of superficial sinuses and deeper cortical veins that drain the superficial surfaces of both cerebral hemispheres and the deeper brain structures ultimately returning blood back to the heart via the internal jugular veins. The cerebral venous
The system is divided into a superficial system (superior sagittal sinus, inferior sagittal sinus, cortical veins) and a deep system (transverse sinus, straight sinus, sigmoid sinus, deeper cortical veins). The flow patterns and anatomy can be seen in Figures 1 and 2.

The superficial cortical veins adhering to the arachnoid layer are thin walled and have no valves [3]. Typical cerebral venous flow starts with the superficial cortical veins draining into the superior/inferior sagittal sinus or straight sinus draining into the confluence of sinuses (also known as torcula or torcular herophili) to the transverse sinuses, sigmoid sinuses, and then internal jugular veins. The superior sagittal sinus drains the superior-lateral cerebral hemispheric surfaces bilaterally. The diploic, meningeal and emissary veins drain into the superior sagittal sinus. This is of clinical importance in scalp and CSF infections as prothrombotic venous drainage into the superior sagittal sinus can induce thrombus formation within that structure. The inferior sagittal sinus drains the bilateral medial cerebral hemispheres as well as the falx cerebri. The inferior sagittal sinus joins with the great vein of Galen to form the straight sinus. The great vein of Galen is formed by the internal cerebral vein (formed by thalamostriate vein, septal vein and choroid vein) and basal vein of Rosenthal (anterior/middle cerebral vein and striate vein) which drain the basal ganglia and deep white matter bilaterally. The lateral sinuses (transverse and sigmoid sinuses) receive drainage directly from the posterior cerebral hemisphere, brainstem and cerebellum bilaterally. Of clinical importance, the anatomical positioning of these lateral sinuses near the mastoid air cells increases their susceptibility to thrombosis formation in the setting of ear infections such as chronic otitis media and mastoiditis [4].

Two unique parts of the venous sinus drainage system are the anastomotic veins and the bilateral cavernous sinus. The superior anastomotic vein of Trolard connects the superior sagittal sinus and the superficial vein of Sylvius. The inferior anastomotic vein of Labbe connects the superficial middle cerebral vein and transverse sinus. The cavernous sinus receives drainage

Figure 1. Cerebral venous anatomy.
from the orbits, inferior frontal lobe, inferior parietal lobe and the face in the nasal region. Given that cranial nerves CNIII, CN IV, CN V-1, CN V-2 and CN VI pass through the cavernous sinus this becomes an important clinical localization point in the setting of facial and nasal infections.

Much of neurology involves pattern recognition in the setting of clinical findings and syndromes. Clinical syndromes of the venous system are less well stereotyped than the more commonly seen and appreciated arterial stroke syndromes. Cerebral cortical veins often have a common presentation of focal seizure activity correlating with the specific region of the cortex involved. Thrombosis involving the deep venous system leads to mental status changes and can progress to coma when the bilateral thalami are involved. Notably, thrombosis involving the deeper venous system generally results in a more rapid deterioration compared to the superficial system. Clinically, thrombosis in the superior sagittal sinus syndrome can present quite variably, but the classic syndrome includes bilateral motor deficits, neurobehavioral issues related to frontal lobe injury, and seizure activity related to hemispheric cortical involvement. Other findings can include scalp and/or face edema, and dilated scalp veins based on the lack of venous flow into the sagittal sinus [5]. Thrombosis in the transverse venous sinus typically results in parietal lobe deficits with patients presenting with either aphasia or neglect depending on hemispheric dominance. Accompanying symptoms often include headaches, ear and/or mastoid pain. The visual pathways can also be affected in a lateral sinus thrombosis syndrome thus resulting in hemianopia secondary to occipital lobe involvement. Cavernous sinus thrombosis typically presents with diplopia, proptosis, headache and orbital pain, or some combination of these, with the examiner eliciting cranial nerve palsies involving CN-III, CN-IV, CN-V1, CN-V2, CN VI.

Figure 2. Cerebral venous anatomy on magnetic resonance venogram (MRV).
3. Epidemiology

CVT, in absolute terms, is an uncommon diagnosis occurring in 5 per 1 million adults every year [1]. In all, CVT accounts for 0.5–1% of all strokes [6]. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) trial, which evaluated 624 patients in 24 countries, subjects had a median age of 37 years old (78% cases <50 years old) with 74% of enrollees being female, illustrating that CVT is generally a disease of young women [3]. The overall incidence of CVT is 1.32 per 100,000 person-years [7]. CVT occurs in women at a higher rate than men, with the women aged 31–50 years harboring the greatest risk with an incidence of 2.78 per 100,000 person-years [7, 8]. Among the young stroke population, CVT accounts for approximately 5% of cases [9].

The incidence of CVT in the Canadian Pediatric Ischemic Stroke Registry (CRISR) was 6.7 per 1 million [10]. A majority (54%) of the children were younger than 1 year old with 45% below the age of 1 month. This patient population will be further discussed in the following section.

4. Pathophysiology

The potential causes for CVT are numerous, but the underlying reason is the coagulation balance is tipped towards a pro-thrombotic state. There are numerous predisposing factors that contribute to the formation of CVT. Examples include medical problems such as thrombophilias, infections and inflammatory states (e.g., autoimmune diseases), transient physiological states including dehydration and pregnancy, medications especially oral contraceptives (OCPs), smoking, and head trauma [11, 12].

The main data on epidemiology of CVT comes from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). An ISCVT study demonstrated that more than 44% of the subjects were identified to have more than one cause to their CVT [13]. In that study the most common contributing factor was OCP use (54%) followed by thrombophilia (34.1%), puerperium (14%), infection (12%), malignancy (7.4%) and pregnancy (6%). These contributing factors give credence to the predilection for women in child bearing years. Specifically, OCP use, pregnancy and puerperium risks are exclusive to that subset of patients. An estimated 2% of strokes during pregnancy can be attributed to CVT [14]. The puerperium period is the first 6–8 weeks after childbirth, and it is in that period where the risk of all venous thromboembolic events is increased, with an overall frequency of CVT estimated to be 12 per 100,000 delivers [15, 16]. Although there is limited evidence, factors that have been associated with puerperium CVT include hyperhomocysteinemia, advanced maternal age, cesarean delivery, maternal hypertension, infections and excessive vomiting during pregnancy [17, 18]. In developing and underdeveloped countries, postpartum strokes are relatively common with contributing risk factors including poor antenatal and postpartum care, home deliveries, anemia, and dehydration. During pregnancy itself, the highest incidence worldwide is during the 3rd trimester [19].
The proposed mechanism for the observed young female preponderance is that hormonal factors create a prothrombotic state. The reason many authors cite this to be true is that the incidence of CVT among elderly and children is sex-independent [10, 20]. More evidence supporting hormonal contribution to the pathophysiology is the association between CVT and ovarian hyperstimulation syndrome [21]. The relative risk of CVT among OCP users was as high as 15.9 in one study [22]. A meta-analysis that examined 17 CVT studies calculated an OR 5.59 increased risk of CVT with OCP use [23]. The effect is synergistic when OCP use is combined with a hereditary prothrombotic factors including factor V Leiden or prothrombin G20210A mutation, with the latter demonstrating an OR of 149.3 in one study [24, 25]. Pregnancy and OCP use, absent genetic conditions, are thought to be transient and thus generally not thought to carry a higher risk of recurrence.

Numerous studies have been dedicated to exploring the association between genetic hypercoagulability and CVT risk. A meta-analysis that reviewed 26 case–control studies including 1183 CVT cases and 5189 controls, demonstrated the two gene mutations that most clearly associated with CVT risk were Factor V Leiden/G1691A (OR 2.40 [1.75–3.30; p-value 0.00001) and prothrombin gene mutation (OR 5.48 [3.88–7.74]; p-value 0.00001) [26]. In the same study, they performed an iterative analysis which showed a statistically significant association with methylene tetrahydrofolate reductase/C677T (OR 2.30 [1.20–4.42; p-value 0.02]. Similar associations were described in systematic reviews that showed statistically significant increases in odds ratio (OR) for prothrombin gene mutation (9.27 [5.85–1467]), Factor V Leiden (3.38 [2.27–5.05]) and hyperhomocysteinemia (4.07 [2.54–6.52]) [27]. In ISCVT 22% of the patients had a genetic hypercoagulable state [13]. In decreasing order of frequency, the identified genes were G20210A prothrombin mutation, Factor V Leiden, anticardiolipin/antiphospholipid antibodies, protein C deficiency, protein S deficiency and antithrombin III deficiency [3, 15, 18, 24, 27–31].

Another acquired hypercoagulable state that is common in the setting of CVT is malignancy. The mechanism by which malignancy causes hypercoagulability is varied. Authors have suggested that potential mechanisms may include tumor invasion of venous sinuses, compression of dural venous sinuses, an imbalance in systemic inflammatory mediators, chemotherapy, and targeted hormone therapy (i.e., tamoxifen for breast cancer treatment) [32–35]. The associated malignancies represented were primary CNS tumors (2.2%), metastases of solid tumors (3.2%) and hematologic malignancies (2.9%) [3].

Infections are another well-established cause of CVTs. Developed countries have shown a decline in infection related CVTs, but in developing countries at ~18% it remains a prevalent cause [36]. In ISCVT infection accounted for 8.2% of adults [37]. Locations of the parameningeal infections were in the ear, sinus, mouth, face and neck. Cavernous sinus thrombosis specifically is overwhelming caused by skin infections of the face and/or nasal sinuses, where the venous drainage flows directly into the cavernous sinus. Another syndrome, called Lemierre’s syndrome, results from oropharyngeal infection leading to thrombosis of the internal jugular vein which may back propagate causing extensive CVT. Further, the localized inflammation may also invade the internal carotid arteries (ICA) as they pass through the oropharynx, thereby leading to arterial strokes.
In children, infection was the most common cause of CVT. Among neonates, infection occurred in 84% of all patients [10]. In patients older than 1 month, the majority of case etiologies shifted towards chronic medical conditions, including connective tissue disorders (23%), hematologic diseases (20%) and cancers (13%) [10].

5. Clinical presentation

CVT is a diagnosis that is often delayed given its variable presentation. ISCVT patients were diagnosed a median of 7 days after symptom-onset, most of whom diagnosed were diagnosed between 48 hours and 30 days from symptom-onset (56%). This time-period was followed by: acute <48 hours (37%), and chronically >30 days (7%). Across all time-periods, the median delay from symptom-onset until admission was 4 days [3, 38, 39]. Interestingly, delay in diagnosis was associated with increased risk of visual deficits [39]. Men and patients with isolated elevated ICP were diagnosed later. It is helpful to consider the two primary mechanisms that cause neurologic dysfunction: (1) increased intracranial pressure (ICP) and (2) hypoperfusion.

The increased intracranial pressure is due to poor venous outflow effectively leading to increased cerebral venous resistance and decreased CSF drainage, thus increasing ICP [40]. The increased ICP generally results in three manifestations: headache, diplopia and papilledema. In ISCVT, almost 90% of patients examined had headache as a presenting symptom. The headaches were generally described as diffuse progressing over days to weeks, with thunderclap headache being the rare presentation [3, 41]. The authors recommended a higher index of suspicion for high risk patients (women of childbearing age especially on OCPs in isolation or in combination with smoking) who have a new and/or atypical headache not responsive to over the counter analgesics [41]. Patients presenting with isolated headaches had a favorable prognosis in one study [42]. Patients not presenting with headache in the ISCVT cohort were older men and were more likely to have cancer [43]. The mortality was higher in that group, but there was no statistically significant difference when adjusting for confounders in the data [42].

In addition, the increased ICP may also lead to papilledema. The clinical symptoms can be transient visual obscurations, transient vision loss, peripheral vision loss and pulsatile tinnitus. Nausea and vomiting are also common. The diplopia is often caused by compression of one or both abducens nerves leading to horizontal diplopia. More directly, cavernous sinus thrombosis may lead to diplopia via localized involvement with the oculomotor and abducens nerves as they pass through the cavernous sinus. Class I, level C evidence in guidelines suggests cerebral venous imaging in patients with clinical symptoms of increased intracranial pressure [38].

The other primary mechanism is venous infarction as related to a combination of hypoperfusion, ischemia and/or hemorrhagic injury. In such instances, focal neurologic syndromes are encountered in the patterns previously described in the previous “Anatomy and Associated Clinical Syndromes” section. Should hemorrhagic and/or ischemic strokes develop, focal neurologic deficits such as aphasia or hemiparesis can be seen. Patients can present with acute
psychosis, typically in combination with other signs and symptoms, but rarely as the sole manifestation. Seizures are also very common, as there is often a disturbed blood–brain barrier with edema development in the setting of viable cortical neurons and supporting cells. Seizures can be focal, unilateral or bilateral, and can also secondarily generalize. In ISCVT seizures were present in 40% of subjects [3].

6. Diagnostic evaluation

After a thorough history and physical examination, the most useful diagnostic tool is imaging. As with most patients, the initial scan will be a non-contrast computed tomography (CT) of the head. The purpose of these initial screening images is to evaluate for signs of ischemia, hemorrhage, a “filled” or hyperdense delta sign and/or other evidence of hyperdense venous sinuses. These are the radiographically important CT imaging findings seen in the setting of CVT. The non-contrast CT is estimated to be abnormal in 30% of individuals with CVT [1, 23, 44–48]. ICH is the initial presentation in 30–40% of CVT patients [49, 50]. The filled delta sign is a triangular hyperdensity in the posterior portion of the superior sagittal sinus in the area of the confluence of the sinuses. A hyperdense dural sign, indicating CVT in a dural vein, is appreciated on approximately 1/3 CVT cases undergoing CT head [44, 45, 47]. Furthermore, the index of suspicion is raised higher if there is hemorrhage that is atypical in appearance, meaning that it is close to venous sinuses and/or crosses typical arterial vascular borders. When patients present with focal neurologic deficits within an acute intervention window (up to 24 hours since last known well in certain circumstances), the recommendation of the authors is to perform an emergent CT angiogram (CTA) with delayed phase CT venogram (CTV) as part of the initial evaluation. These studies evaluate patients for large-vessel arterial occlusion, with the CTV performed primarily to evaluate for collateral flow in the setting of potential mechanical thrombectomy. However, an added benefit of the delayed phase CTV is that one is also able to evaluate for venous thrombus. Anecdotally, the authors have discovered CVT in the initial CT/CTA/CTV approach in patients with hemorrhagic strokes presenting acutely. A dedicated CTV evaluates the venous sinuses themselves, which would demonstrate thrombosis if present. Some suggest that CTV is more valuable in the subacute and chronic phases because it shows varying density of the thrombosis within the sinuses [38].

MRI is also helpful in the evaluation of CVT. In addition to ruling in or out other diagnoses on the differential, including brain tumors for example, it can provide helpful information for confirming CVT. Consistent with the non-contrast CT brain, the pattern and location of injury can be helpful if hemorrhage or ischemia is present. Parenchymal damage can manifest as ischemia (restricted diffusion), edema and hemorrhage. Edema without hemorrhage is more easily detected on MRI versus CT brain (25% versus 8%) respectively [10, 44, 46, 51–57]. Hemorrhage-specific MRI sequences are positive in up to 40% of CVT patients [44, 51, 53, 57–60]. The pattern of parenchymal injury often provides clues to the venous structures involved. For example, simultaneous injury involving the frontal, parietal and occipital cortices would correspond to a superior sagittal sinus thrombosis. Transverse and sigmoid sinuses result in temporal lobe injury. Deep structures are injured in thrombosis of the straight sinus.
and/or vein of Galen. MRI T2 weighted sequences can provide insight into the venous sinuses themselves, with absent flow voids manifesting as T2 hypointensities. Such findings, can be suggestive of CVT especially with accompanying parenchymal changes discussed above. Although uncommon, hyperintense cortical veins on T2 sequences can be used to identify isolated cortical vein thrombosis [51, 61–68].

If CVT is clinically suspected, dedicated venous imaging is required, even if the initial plain brain CT brain or brain MRI were negative. As discussed, CTV can be used, however MRV is another option. MRV reveals loss of flow signal in the venous sinuses [69]. This can be especially helpful when combined with above modalities. In our practice, we use susceptibility weighted imaging on MRI to help augment diagnostic accuracy in combination with MRV.

DSA is indicated in patients with parenchymal changes (edema and/or hemorrhage) without conclusive venography on CTV or MRV. A 4-vessel DSA will help evaluate for possible arterial etiologies to the observed parenchymal damage, however the late-phase contrast runoff can be used to examine the venous system. As another option, some authors suggest direct venography via micro-catherization of the internal jugular vein [70, 71]. Such a technique might be useful if an intervention is being considering.

From a serology standpoint, D-dimer has an excellent negative predictive value (99.6%), which is helpful in identifying patients with low probability of having CVT [72, 73]. In one prospective multicenter trial, D-dimer had a specificity of 91.2% and sensitivity of 97.1% [72]. There was a smaller study that found that the false negative rate was 10% in patients presenting with isolated headache [73]. Interestingly, there was a positive correlation with D-dimer level and extent of CVT, and negative correlation with duration of symptoms [72–77].

After the diagnosis is established it is important to identify the etiology. Recommended lab tests as per evidence-based guidelines in the acute setting include: complete blood count (CBC), complete metabolic panel (CMP), prothrombin time (PT) and activated partial thromboplastin time (aPTT). Hypercoagulable testing for protein C, protein S, antithrombin, anticardiolipin and antiphospholipid antibodies, prothrombin G20210A mutation and factor V Leiden [38, 78–82] are also valuable and should be considered early. In the setting of anticoagulation use, only antibody and genetic tests are possible. If infection is considered, blood cultures should be attained. In certain populations, it is not unreasonable to perform a malignancy screen with CT chest, abdomen and pelvis ± testicular ultrasound.

7. Treatment

Patients who are suspected of having CVT benefit from evaluation by a vascular neurologist and being admitted to a stroke unit [83, 84]. Once a CVT is confirmed, the goal of therapy is to initiate anticoagulation quickly with the goal of preventing thrombus propagation. The data for CVT is certainly not as robust as many other areas of stroke therapy with a total of 12 published studies to date [3, 40, 49, 55, 85–94], with only 2 randomized-prospective-controlled trials [40, 85].
The first study evaluating CVT treatment was published in Lancet [85]. This double-blind placebo-controlled trial aimed to shed light on the ongoing treatment controversies at that time in clinical practice [85]. The prevailing thought that anticoagulation frequently caused ICH. The study included 20 patients with aseptic CVT randomized to anticoagulation versus placebo. The anticoagulation arm consisted of a heparin bolus of 3000 international units (IU) followed by continuous infusion adjusted to goal PTT 2× the pretreatment value. The primary outcome measure was a CVT severity scale which considered headache, focal signs, seizures and level of consciousness. The secondary outcome was ICH. The study was powered to evaluate 60 patients; however, enrollment was stopped at 20 given the clear benefit of treatment with anticoagulation at the interval analysis. The heparin group showed statistically significant benefit (Mann-Whitney U test p < 0.05) comparing the primary outcome at day 3 and day 8 (p < 0.01). At 3 months 8 patients in the treatment arm had complete recovery and 2 had slight neurologic deficits. In the placebo group 1 patient had complete recovery, 6 with neurologic deficits, and 3 patients were deceased. Notably, none of the treatment group patients developed ICH.

The larger of the two RCTs enrolled patients in the United Kingdom and Netherlands between 7/1992 and 11/1996 [40]. The entire population included 59 patients who were confirmed to have CVT using MRI, MRV and/or angiography. These were adult patients (≥18 years old) with the major exclusion criteria including pregnancy, contraindications for heparin use, poor baseline prognosis, increased ICP requiring lumbar puncture (LP) or shunt. The two arms evaluated nadroparin (190 units/kg/24 hours) versus placebo. After 21 days the blinding was broken and patients in the treatment arm got 10 weeks of warfarin with an international normalized ration (INR) goal 2.5–3.5. The placebo group did not receive anticoagulation or have sham bloodwork. The primary outcome was the Barthel index (BI) at 21 days expressed as a percentage, with a poor outcome defined as BI >15. Notable baseline characteristics for enrolled patients included: a mean age of 36.9 years old (range 18–80), 85% female, delay to randomization 10.6 days, 95% with recent headache, 47% with seizures, 96.6% with a focal neurologic deficit and 49% with cerebral hemorrhage. After 3 weeks, the anticoagulation arm was shown to have poor outcome in 20% of patients versus 24% for placebo, which was not statistically significant. At 12 weeks a secondary evaluation of poor outcome was performed, defined as death or Oxford Handicap Score ≥ 3. Poor outcomes were shown in 13% of anticoagulation group versus 21% of placebo group (risk difference 27% [−26–12%]) which was also not statistically significant. The primary take home point per the study investigators was that there was no new hemorrhage, this, even in the treatment group. As such, anticoagulation was deemed safe despite the presence of cerebral hemorrhage at the time of CVT presentation. Although, the presence of cerebral hemorrhage at presentation was associated with mortality in the study. Notably, the lack of increased frequency of new ICH while receiving anticoagulation therapy is in agreement with other studies that demonstrating low hemorrhage rates after initiation of anticoagulation in the setting of CVT [85, 88].

In the setting of CVT, a non-randomized prospective cohort study compared the efficacy of unfractionated heparin (UFH) versus low molecular weight heparin (LMWH); 302 patients received UFH versus 119 patients received LMWH [95]. The primary endpoint was functional
independence at 6 months defined as modified Rankin score < 3. More patients in the LMWH arm were functionally independent after 6 months (92% versus 84%). This was statistically significant in univariate (OR 2.1 [1.0–4.2], p 0.04) and multivariate adjusted analysis (OR 2.4 [1.0–5.7], p 0.04). There was no statistically significant difference in the main secondary endpoints, which included: complete recovery — measured as a modified Rankin Scale (mRS) 0–1, mortality, and new intracranial hemorrhage. Another study, performed in India, further substantiated the claim that LMWH has a benefit in hospital mortality as compared to UFH [96].

The most recent guideline recommendations are that patients with confirmed CVT should be given anticoagulation initially with either UFH or LMWH followed by warfarin offered as class IIa and level of evidence B [40, 85, 88, 92, 97, 98]. There are no large studies evaluating the efficacy of direct acting oral anticoagulants (DOACs) in CVT, as such, warfarin is generally preferred. However, there are occasions when the authors consider and do initiate DOACs/NOACs, including patient preference and in the setting of warfarin interactions with other medications [99, 100].

7.1. Rescue therapies: endovascular intervention

Endovascular intervention is considered when there is clinical deterioration despite anticoagulation [101–110]. These patients often have clot propagation leading to further infarction or hemorrhagic injury, worsening ICP elevated due to poor venous outflow, or a combination of these factors. One of the approaches for so-called rescue therapy in CVT is delivery of intra-sinus thrombolytics. At present, there are no randomized, double-blinded, placebo-controlled trials evaluating the efficacy of intrasinus thrombolysis. This procedure is rarely performed and would be best referred to a large academic center with robust interventional neuroradiologic experience [103].

A systematic review evaluated at total of 26 patients undergoing intrasinus thrombolysis including 80.8% with superior sagittal sinus thrombosis and 19.2% with deep sinus involvement [104]. Urokinases were used in 73.1% of the cases, followed by streptokinase (7.7%), with the remainder utilizing recombinant tissue plasminogen activator (rTPA). Radiographic success of recanalization was attained in 61.5% patients, with 88% attaining a mRS 0–2 at last available follow up. Complications included ICH in 11.5% of cases, extracranial hemorrhages in 19.2%, and 2 deaths (7.7%).

Another 29 patients were evaluated in a series conducted from 4/2013 to 4/2016 all of whom were treated with in-situ tPA with the tPA delivered directly into the venous sinus via micro-catheter [105]. The radiographic success of recanalization was 100% in this series, of which 82.8% had favorable outcome (mRS 0–1), 10.3% mRS of 2, and 3.4% (1 patient) died.

Another prospective case series evaluated patients with CVT who underwent intrasinus thrombolysis among patients with altered mental status, coma, straight sinus thrombosis, or large space occupying lesions [106]. The population included 20 patients (80% women, mean age 32 years old) who received infused urokinase via internal jugular catheter. Clinically 60% of patients were comatose and 70% had hemorrhage prior to treatment. In 75% of patients the thrombolysis was coupled with mechanical thrombus disruption or removal. Post intervention
the mortality rate was 30% (6 patients), 5 of whom had large hemispheric infarcts and edema prior to intervention. Ultimately an mRS of 0–2 was achieved in 60% of cases.

Another study evaluated 37 CVT patients between 1/2007 and 12/2009 who underwent intrasinus urokinase infusion thrombolysis using a microcatheter [107]. At 6-month follow up, radiographic canalization was obtained in 97% of patients, with functional outcome rates of mRS 0–1 (75.8%), mRS 2 (18.2%), mRS 4 (3.0%), and a 3.0% mortality rate (mRS 6).

Another rescue therapy utilized is mechanical thrombectomy. One systematic review evaluated patients from 42 studies treated between 1/1995 and 2/2014 undergoing mechanical thrombectomy with or without intrasinus thrombolysis [108]. The review included a total of 185 patients with CVT, 62% of whom had ICH prior to intervention. Clinically 47% were either stuporous or comatose. The most commonly used interventional device for mechanical thrombectomy was an AngioJet, used in 40% of the cases, although it was associated with a lower complete recanalization rate (OR 0.2 [0.09–0.4]) and lower chance of mRS 0–2 (OR 0.5 [0.2–1.0]) as compared with other therapies. A total 71% of these patients also underwent intrasinus thrombolysis. A mRS 0–2 was observed in 84% of patients and the mortality rate was 12%. At least partial recanalization was obtained in 95% of cases. The major complications included new or increased ICH in approximately 10% of the cases.

Another systematic review in BMJ evaluated 17 studies totaling 235 patients [109]. Intrasinus thrombolysis was used in 87.6% of patients. Radiographically complete revascularization was achieved in 69% of patients, with a mortality rate of 14.3%, 1.2% recurrent CVT rate, and a new or worsening ICH rate of 8.7%.

Another review evaluated CVT patients undergoing mechanical thrombectomy between 1990 and 2012 [110]. A total of 64 patients underwent mechanical thrombectomy with different techniques including AngioJet (46.9%), Penumbra (4.7%), Fogarty catheter (1.6%), microsnare (3.1%), balloon venoplasty without stenting (18.7%), balloon venoplasty with stenting (4.7%), and a combination approach (18.7%). The mortality rate in this review was 16.1%. The morbidity data showed mRS 0–2 (62.5%), mRS 3–5 (10.9%) and 12.5% were unreported.

7.2. Decompressive surgery

Patients with CVT are at risk of herniation syndromes due to multiple factors as related to mass effect. Herniation is a major cause of death in CVT, thus decompressive surgery is an important option in the treatment armamentarium. Herniation is generally due to large ischemic regions and/or large hematomas. One study evaluated the safety and efficacy of decompressive surgery in a retrospective fashion by evaluating a registry of acute CVT patients [111]. A total of 69 patients were included in the study, 45 underwent decompressive craniectomy, 7 underwent hematoma evacuation, and 17 received both therapies. The primary outcome was mRS at last follow-up analyzed in dichotomously (favorable mRS 0–2 versus unfavorable mRS 5–6). In median 12-month follow-up 17.4% had an unfavorable outcome. This also resulted in favorable functional outcomes in the secondary analysis demonstrating 37.7% with near complete recovery (mRS 0–1), 56.5% (mRS 0–2), 5.8% (mRS 4–5), and a 15.9% mortality rate. As consistent with decompressive surgery in arterial ischemic stroke, it
is important to treat early, before patients decline into a comatose state. As demonstrated in the just described study, patients who were comatose were less likely to be independent mRS <2 than non-comatose patients (45% versus 84%, p-value 0.003).

7.3. Seizures

Seizures are very common at presentation among patients with CVT. One prospective observational study found seizures in 39.3% of CVT patients and 6.9% of patients had early seizures (within 2 weeks) [112]. Factors associated with seizures at presentation were supratentorial lesions, cortical vein thrombosis, sagittal sinus thrombosis, and puerperal CVT. Beyond seizures at presentation, supratentorial lesions were also a predictor of early seizures. Patients who suffer a seizure at presentation, or in the early phase of CVT, should be treated with antiepileptics for prevention of further seizures, this, whether a parenchymal lesion is seen on imaging or not. Currently, it is not recommended to treat prophylactically in the absence of a seizure. However, patients with acute and florid CVT are quite prone to seizures, with the occurrence of even a single seizure potentially negatively impacting outcome. Hence, in such situations, initiating a short course of antiepileptic drugs is highly reasonable and should be considered. As a general guideline, the authors treat for 14 days when there is one isolated seizure at presentation or early in the course. If there is more than one seizure the authors will treat for 3–6 months and discontinue therapy if no additional seizures occurred outside the acute phase. One observational study provides some evidence supporting prophylactic AED treatment in the setting of supratentorial lesions in the absence of seizures reporting 1 seizures in 148 patients treated with AEDs versus 25 in 47 patients without AEDs (OR 0.006 [0.001–0.05]) [112].

7.4. Increased intracranial pressure

Obstruction of the venous sinuses will increase the intracranial pressure (ICP). Common symptoms include headache and papilledema. Patients who experience papilledema and visual disturbances need to be monitored closely for further decompensation of visual fields. In the event symptoms, acetazolamide can be initiated with similar dosing to idiopathic intracranial hypertension (IIH). The authors generally initiate therapy at 500 mg twice a day and up-titrate as needed for therapeutic efficacy. If additional supplementation is needed, or for prophylaxis, the authors generally use topiramate titrated to efficacy with maximum daily dose being 200 mg total in 2 equally-divided doses. Abortive headache management approaches start conservatively with acetaminophen followed by ibuprofen or other NSAIDs (i.e., ketorolac), then tramadol, opioids and lastly migraine cocktails.

The treatment of emergency vision loss requires rapid, but careful consideration. Possible etiologies include elevated ICP or retinal ischemia. Treatment options for elevated ICP in a correlated disease, idiopathic intracranial hypertension (IIH), include optic nerve sheath fenestration and ventriculoperitoneal shunt procedures. The issue unique to CVT is the fact that the underlying visual loss etiology is due to venous obstruction and/or congestion. Thus, there are circumstances where it would be beneficial to evaluate if the venous outflow is completely obstructed, thereby leading to retinal flow stasis and subsequent retinal ischemia.
In that case, the authors would advocate serious consideration of interventional clot extraction to restore venous flow and thus decrease ICP. This is based on opinion. Guidelines do cite LP, optic nerve decompression, and shunts as possible treatment options but do not delineate timing of these procedures in relation to rescue revascularization therapy. Deep venous system or cavernous sinus thromboses progressing to occlude retinal outflow tracts are particularly worrisome. These etiologies can cause permanent blindness and should be considered in the setting of acute vision loss. An urgent ophthalmological evaluation in such situations is highly warranted.

Lumbar punctures (LP) are not required in the diagnostic evaluation of CVT. However, if ICP measurement is necessary, it is safe to do an LP even in the acute phase [113]. The expected CSF chemistry profile is a pleocytosis (50%) and an elevated protein (35%) [3], but these CSF abnormalities are not specific to a CVT diagnosis. LP is generally used to measure ICP and/or to evaluate for other underlying etiologies (e.g., infection).

7.5. Special considerations

7.5.1. Pregnancy

The ISCVT cohort evaluated 119 women for a median follow up time of 14 months with a total of 82 pregnancies occurring among 47 women [114]. Recurrent venous thrombotic event (VTE) occurred only in 3 of the 82 pregnancies (1 of which was recurrent CVT). A majority, 83%, of the total cohort received prophylactic DVT treatment during at least one trimester, including 2 of the 3 patients that had a VTE event. The outcomes of the pregnancies were as follows: 51 full-term newborns, 9 preterm births, 2 stillbirths, and 20 abortions (14 spontaneous). CVT patients who are pregnant or become pregnant are recommended to continue anticoagulation. Warfarin is not recommended because of its teratogenic effects. In these cases, the authors recommend using enoxaparin throughout the duration of pregnancy. LMWH is preferred over UFH. Guidelines also suggest continuation with either LMWH or warfarin 6 weeks postpartum [38]. If this becomes problematic, then the authors would consider the use of DOACs with the preference being apixaban in patients with normal renal function.

In women of childbearing age, especially those who had a CVT due to OCP use, it is recommended that the women use contraceptive methods without hormonal components. Generally, this is intrauterine device (IUD) therapy. Sometimes emergency contraception is indicated [115]. CVT does not preclude one from getting pregnant in the future but should be monitored closely in a high-risk pregnancy clinic as dictated by an obstetrician. Collaboration between the neurologist and obstetrician is recommended. The decision for prophylactic therapy during subsequent pregnancies should be done on an individual patient basis. However, the authors generally recommend daily prophylaxis with enoxaparin especially in the third trimester.

7.5.2. Infections

Analysis of the ISCVT cohort revealed that new ICH was more frequent in patients with infection as the etiology of their CVT [116]. The study compared infected versus noninfected
patients, with infected patients representing 9.4% of the cohort. New ICH occurred in 12.3% versus 5.3% \((p-value \ 0.04)\) within similar rates of heparin use in each group. Notably, there was no difference in death or dependency between the two groups.

7.5.3. Steroids

A subset (24%) of patients in ISCVT received steroids in the acute CVT phase. Steroid use in the acute phase is not clinically beneficial. Hence, steroids are not used in the setting of CVT.

7.5.4. Pediatrics

The approach to children with CVT is similar to adults. However, because children often have an infectious component to their CVT, much of the diagnostic evaluation should also include evaluations for infection [117–119]. Patients beyond 28 days old are recommended for acute therapy with LMWH and they should continue anticoagulation for 3–6 months (warfarin) [38]. Neonates should be considered for anticoagulation on a case by case basis. In pediatric patients, one should have a lower threshold to evaluate with EEG.

8. Prognosis and long-term follow-up

Many studies demonstrate a CVT recurrence rate between 2 and 5% [3, 7, 120–122]. Other VTE was demonstrated in 4.3–8% of patients in those studies. The ISCVT recurrence rate for CVT was 1.5 per 100 person-years, or 2.2% [123]. In the ISCVT study, mortality was 8.3% at 16 months [3]. A majority of patients (79%) had complete recovery defined as mRS 0–1, 10.4% with mRS 2–3, 2.2% with mRS 4–5. Bilateral lesions were associated with unfavorable outcomes (50% versus 11%, \(p \ 0.004\)) and death (42% versus 11%, \(p \ 0.025\)) [111]. A previous VTE was a predictor of recurrence but not secondary or unprovoked CVTs [122]. Recurrence tended to occur within a year of the first CVT [3]. CVT has lower mortality and morbidity in comparison to other stroke types [1, 2]. Factors associated with poor outcome were older age, malignancy, CNS infection, and ICH [1]. Gender was not associated with poor outcomes after adjustment [8]. Independent predictors of death in the ISCVT were reported to include coma, mentalational disturbances, deep CVT, right hemispheric ICH, and posterior fossa lesions. Causes of death were either transtentorial herniation or diffuse edema [13]. In a national database from 2000 to 2007 the mortality rate was 4.39%. The mortality predictors in this study were older age, ICH, hematologic disorders, systemic malignancy and CNS infection [124].

Prognostic information was evaluated in the ISCVT patient cohort. With a median follow-up of 16 months, 57.1% had a mRS of 0, signifying no symptoms, while 8.3% died. The multivariate analysis identified statistically significant predictors of death and disability to include age > 37 years (hazard ratio (HR) 2.0), male sex (HR 1.6), coma (HR 2.7), GCS <9 (HR 2.65) hemorrhage on admission CT scan (HR 1.9), thrombosis of the deep cerebral venous system (HR 2.9), central nervous system infection (HR 3.3), and cancer (HR 2.9) [125]. Another study looked at the predictors of CVT outcome in patients with ICH, this in the ISCVT cohort [49].
Early ICH was defined as ICH present at time of CVT diagnosis. A logistic regression analysis was performed using mRS 3–6 as dependent variable. The patients with early CVT represented 39% of the CVT population at month 6. The independent predictors of death or dependency at 6 months with early ICH in CVT included: older age (adjusted OR for 1-year increase in age, 1.05 [1.02–1.08], male gender (adjusted OR 3.25 [1.29–8.16]), deep CVT (adjusted OR 5.43 [1.67–17.61], right lateral sinus CVT (adjusted OR 2.56 [1.03–6.40] and motor deficit (adjusted OR 2.94 [1.21–7.10] [49].

9. Conclusions

CVT is a less common, but highly treatable, cause of stroke accounting for 0.5–1% of all strokes with a preponderance to occur in women. Our goal was to provide clinicians with the knowledge to rapidly diagnose CVT with an emphasis on etiologies and treatments in an effort to produce optimal clinical outcomes. Clinicians must possess a working knowledge of the relevant anatomy and associated clinical syndromes, and be aware of the relevant clinical trials as described herein. Clinicians must consider CVT when evaluating patients suffering with acute neurological changes, particularly those with predisposing risk factors such as OCP use, smoking, and a postpartum state, among others.

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