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METHODS

Intracranial venous sinus thrombosis: Medical and surgical management considerations

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Cerebral venous thrombosis is a serious neurological condition characterized by thrombus formation in the venous sinuses or cerebral veins. Although rare, it is a potentially fatal condition that requires prompt diagnosis and treatment. This review aims to present the most current trends in our understanding of CVT risk factors, diagnosis, medical management, role of endovascular management, risk of intracranial hemorrhage, and emerging therapies. Most cases of CVT are diagnosed by clinical features and neuroimaging suggestive of sinus occlusion. While anticoagulation with heparin is the mainstay of medical management, direct-oral anticoagulants are emerging as a potential alternative, and severe cases have been managed successfully with thrombectomy and/or intrasinus urokinase thrombolysis. Despite recent advances in anticoagulation therapy and diagnostics, larger randomized studies are required to adequately assess these emerging therapies and better inform the management of patients suffering from CVT.

Keywords: cerebral venous sinus thrombosis, heparin anticoagulation, intracranial hemorrhage, thrombectomy, thrombolysis

1. Introduction

Cerebral thrombosis (CVT) is a neurologic condition that occurs when a blood clot forms inside either the venous sinuses of the brain or the cerebral veins themselves. CVT is a rare condition affecting approximately 3 persons per million but is a highly fatal diagnosis without prompt recognition and treatment. The history of CVT as a recognized disease state can be dated as far back as 1825 to a post-mortem analysis of a patient who experienced severe seizures and altered mental status (1).

Until the advent of venous imaging, the condition's broad etiology and spectrum of presentations could not be effectively narrowed down. In the modern era, much research has shown a highly heterogeneous condition in etiology and presentation. Specifically, CVT is thought to result from a multifactorial derangement in normal cerebral venous outflow and can involve infectious, hydration status, medication, or genetic contributions. Diagnosis has shown to be among the most misdiagnosed in the clinical neurosciences, as its heterogeneous presentation can be in both young and the old, as well as its symptomology of focal or global cerebral deficits (2–4). It is thus imperative to continue defining and categorizing the spectrum of this condition as new research emerges to improve diagnosis rates and thus time to treatment and ultimately outcomes.

The hallmark of treatment for CVT has been anticoagulation with heparinized agents since the mid-20th century, focused on limiting the recycling of a new clot while the body's endogenous thrombolytic factors break down the clot. Prognoses continue to improve over the modern era with evolving neurosurgical care, particularly the advent of mechanical thrombectomy, and new therapeutic options are under investigation. This review aims to cover the spectrum of CVT, from etiology to surgical treatment, with a look toward the future regarding novel therapeutics in the modern era.

2. Etiology

A majority of patients diagnosed with CVT have at least one previously described risk factor as reported by the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a prospective international observational study (5, 6). These risk factors can be broadly organized into either genetic or acquired. Common genetic risk factors for CVT are antithrombin deficiency, Factor V Leiden mutations, protein C/S deficiency, or hyperhomocysteinemia (7, 8). Acquired risk factors for CVT include oral contraceptive use, hypercoagulable state during pregnancy, underlying malignancy, or infection (9, 10). It is not uncommon for patients diagnosed with CVT from acquired risk factors to have an underlying genetic predisposition that contributes to thrombus formation. While there are a wide range of pathologies (e.g., autoimmune conditions and sickle cell anemia) and risk factors that have been associated with CVT, we will focus on the most implicated risk factors in adults. The overview of etiological risk factors discussed in this review is summarized in **Figure 1**.

2.1. Genetic risk factors for CVT

Marjot et al. (7) conducted a meta-analysis to determine genes most associated with CVT and found that Factor V Leiden [odds ratio (OR) = 2.4, 1.7–3.3, $P < 0.00001$] and prothrombin ($OR = 5.48$, 3.88–7.74, $P < 0.00001$) were associated with CVT in adults. Homozygous methylene tetrahydrofolate reductase (MTHFR) polymorphisms ($OR = 1.83$, 0.88–3.8, $P = 0.09$), which result in hyperhomocysteinemia also showed a modest association with CVT although it failed to reach significance. Green et al. (11) conducted a meta-analysis to determine genetic and non-genetic risk factors for CVT. Similarly to the results obtained by Marjot et al., Factor V ($OR = 1.93$–3.27, $P < 0.001$) and prothrombin polymorphisms ($OR = 3.98$–7.69, $P < 0.001$) were associated with a significantly increased risk of CVT. Interestingly, this meta-analysis also found an association between the risk of CVT and MTHFR polymorphisms ($OR = 1.35$–3.32, $P = 0.001$), however, the authors observed a significant association only after two studies were excluded leading to greater interstudy homogeneity. This point supports the notion that while evidence exists corroborating MTHFR's role in CVT, there exists conflicting evidence due to differences in populations, study design, and confounding variables. A study examining these risk factors in a Tunisian population found strong associations with Factor V ($OR = 2.3$–16.5, $P < 0.001$) and

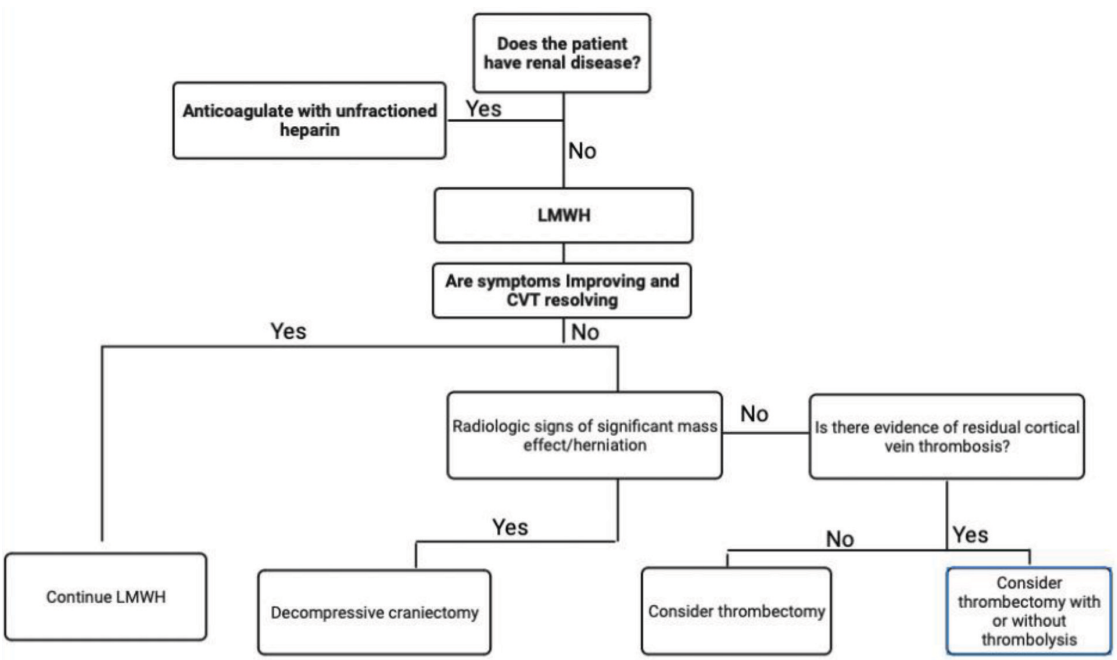

FIGURE 1 | Summary of risk factors for cerebral venous thrombosis.

prothrombin gene mutations but failed to see an association with MHTFR mutations (p = 0.325). (12) Overall, current evidence strongly supports an association between CVT and Factor V and prothrombin mutations. These findings are reasonable given that these factors are inherently related to the regulation of the coagulation cascade. However, the evidence is less clear, regarding MHTFR and some other gene mutations. The heterogeneity of reported studies and mutations in the patient population may render it difficult as these polymorphisms can constitute a wide spectrum of clinical phenotypes and are often complicated by acquired risk factors.

2.2. Hormonal dysregulation

Oral contraceptive use is known to increase the levels of circulating plasma fibrinogen and coagulation factors (13). Physiologic changes during pregnancy render increases in fibrinogen and other coagulation factors as well that correlate with increasing gestational age (14). In a recent case report presented by Aldraihem et al., a 37 year-old male who utilized topical hormones was found to have an underlying CVT with no other known risk factors (15). These reports further bolster the association of hormones on risk for CVT, beyond just systemic venous thrombosis.

2.3. Malignancy

CVT in the context of malignancy is rather rare, comprising less than 1% of patients with cancer (16, 17). Pinto et al. conducted a retrospective review of 111 cases of CVT. They observed that 7 of these patients also had an underlying malignancy, all of which were hematological (18). A case report describes a 60 year-old woman who was found to have a subacute thrombosis of the right transverse sinus, with associated symptoms of CVT (i.e., worsening headache and visual disturbances) (19). This is corroborated by data obtained from a multicenter study examining clinical parameters that are associated with CVT recurrence (20). The authors report that male gender and myeloproliferative neoplasm were associated with CVT recurrence (RR = 2.29–37.76, P = 0.002).

2.4. Infection

While infections may represent a risk factor for CVT, its incidence is decreasing as we have developed a more robust antibiotic arsenal, somewhat relieving the burden of septic thrombus on healthcare resources (21). They are routinely managed with anti-thrombotic therapy or surgical intervention depending on the extent of the infection.

2.5. CVT in the context of the coronavirus disease (COVID)-19 pandemic

The coronavirus pandemic has led to the development of safe and effective vaccines to help prevent severe disease and decrease overall transmission of the virus via herd immunity. Despite its incredibly safe profile, reports of rare cases of thromboembolic events have emerged following either COVID vaccination or infection (22–27). There are several types of COVID-19 vaccines available, which include the mRNA vaccines and adenovirus vector vaccines (28). Of note, the adenovirus vector vaccine ChAdOx1 nCoV-19 has been implicated in the development of thrombocytopenia and thrombosis (29). This pathophysiology of these occurrences is thought to arise from antibodies against platelet factor 4 (30). In fact, levels of anti-PF4 antibody have also been implicated in the overall severity of COVID-19 infection. Kataria et al. reported on a case of immune thrombocytopenia and cerebral venous sinus thrombosis in a young woman 12 days following vaccination against COVID-19 (31). A systematic review of the literature by Sharifian-Dorch et al. revealed that the majority of patients suffering from CVT following COVID-19 vaccination were women and symptom onset generally occurred within a week following the first dose of vaccine (32). A literature review conducted by Mani and Ojha also found that the majority of cases of CVT following COVID-19 vaccination were in female patients (67.4%) consistent with previous reports. The authors also observed that the mean time from vaccination to the thrombotic event was approximately 10 days. Although this study was not specific to CVT, it highlights the rare association between vaccination and embolic events. Given the rarity of these events following vaccination, more robust studies on an international scale would be required to better understand this rare phenomenon.

3. Diagnostics

Clinical features of CVT include headaches, nausea, vomiting, intracranial hypertension, seizures, and focal neurological deficits (33–36). The onset of symptoms is likely to be acute or subacute, with chronic onset reported in a minority of patients. The next step after clinical suspicion of CVT includes immediate neuroimaging. Non-contrast computed tomography (CT) of the brain is often the first-line imaging modality used to rule out other concerning pathologies (37). Hyperdensity of venous structures is a radiographic sign of CVT (38). The most commonly affected venous structure is the transverse sinus (61%) (5). In up to 30% of cases, a CT scan is normal. When combined with CT venography, studies report increased accuracy (39). While useful, CT-based imaging modalities are limited by their inherent radiation exposure and low resolution compared to magnetic resonance imaging (MRI) modalities (40). MR

venography (MRV) is a reliable imaging tool for diagnosing CVT and can be utilized without the need for contrast agents (41). Time-of-flight MRV has been described as a method for CVT diagnosis (42). It is based on the interpretation of absent flow in cerebral venous sinuses but is subject to high variability based on the subject anatomy (42). Furthermore, although uncommon, digital subtraction angiography can be utilized when MRI and CT imaging prove inconclusive (42).

4. Medical anticoagulation management

4.1. Heparin administration

Untreated CVT can be fatal, and patients should be treated immediately following diagnosis. Current treatment options include endovascular intervention and medical anticoagulation (43). Medical anticoagulation therapy consists of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) before starting warfarin (44, 45). In a non-randomized prospective cohort, Coutinho et al. (46) reported that patients treated with LMWH were more likely to be functionally independent [modified Rankin scale (mRS) $\leq$ 2] 6 months post-treatment compared to those administered UFH (92 vs. 85%). Findings were similar when adjusted for prognostic factors (adjusted *OR* = 2.4, 1–5.7). In cases of severe renal impairment, UFH is advised (6).

4.2. Direct-acting oral anticoagulants

Direct-acting oral anticoagulants (DOACs) are coming into favor as an alternative to heparin and vitamin K inhibition. Examples of these agents include dabigatran, rivaroxaban, and apixaban. In a recent case series and systematic review, the authors found that of 19 patients treated with apixaban for CVT, there were no deaths or cases of intracerebral hemorrhage. Investigators also reported no recurrence of CVT and that 95% of patients had a modified Rankin score of $\leq$ 2 post-treatment initiation (47). Similarly, Lurkin et al. conducted a retrospective review of 41 patients following either standard therapy with oral vitamin K antagonist (VKA) (61%) vs. DOACs (39%) (48). The authors reported no major differences in bleeding rates and at the last follow-up ∼66% of DOAC-treated patients vs. ∼33% of VKA-treated patients had good clinical outcomes based on modified Rankin scores. Despite encouraging results, many of these studies are limited by sample size and their retrospective design, signaling the need for larger, multicenter randomized control studies. Anticoagulation modalities can be seen in **Table 1**.

5. Intracranial hemorrhages in cerebral venous sinus thrombosis

CVT accounts for approximately 0.5% of all stroke (49). Thrombosis obstructs cerebral venous outflow and increases intradural and intravenous pressures, which ultimately cause venules to rupture. Infarcted venous territories may also undergo hemorrhagic conversion. Reliable data regarding the rates of intracranial hemorrhage (ICH) in the setting of CVT are scarce and largely derive from single-center and single-country retrospective studies. Older age, male sex, and thrombosis of the deep venous system are independent predictors of a poor outcome in patients with and without evidence of ICH at the time of presentation (5, 49, 50).

Before the 1991 randomized control trial by Einhäupl et al., anticoagulant use in patients with CVT was considered highly controversial out of fear of hemorrhagic conversion. On the basis of this 20-patient trial, heparin is now a widely-accepted as a first-line therapy for CVT, even in the setting of ICH (42, 51). An important subsequent trial improved upon the critiques of the 1991 trial with a larger sample size (59 patients vs. 20), shorter time to treatment from symptom-onset (mean 10.6 days vs. 32.5 days), and a greater proportion of patients with pre-existing ICH (49 vs. 25%) (52). No patients in the Cerebral Venous Sinus Thrombosis Study Group trial experienced new ICH in either group. A Cochrane review of both trials found that 43 patients had pre-existing intracranial or subarachnoid hemorrhage. No new hemorrhages developed in patients treated with anticoagulation, while two hemorrhages were observed in

TABLE 1 | Historical basis for anticoagulant therapy in CVT and summary of reported ICH rates.

Author, year	Study type	Comparison	Intracranial hemorrhage rate		
			Spontaneous	Intervention	Total
Einhäupl et al. (45)	Randomized control trial	IV heparin vs. placebo	20%**	0%	10%
De Bruijn and (52)	Randomized control trial	Subcutaneous LMWH vs. placebo	0%	0%	0%
Ferro et al. (54)	Retrospective	Combination anticoagulation vs. no AC	7.8%	20%**	4.2%
Brucker et al. (55)	Retrospective	IV heparin only	N/A	2.4%	2.4%
Wingerchuk et al. (56)	Retrospective	Combination anticoagulation vs. no AC	33%	0%	17%

**Low number of patients relative to the comparison group. IV, intravenous; LMWH, low-molecular-weight heparin; AC, anticoagulation.

the placebo group, suggesting that treatment with LMWH is likely beneficial for patients with CVT and the risk for ICH in patients with baseline hemorrhagic lesions is low (53). To recapitulate the treatment effect observed in the meta-analysis of both trials, nearly 300 patients would need to be enrolled. Therefore, no similar subsequent randomized trials have followed.

Evidence stemming from retrospective case series also supports low observed rates of ICH (<5%) and even lower rates of systemic hemorrhage (< 2%) in patients with CVT. An 18 year, multi-centric Portuguese cohort of 142 patients found no statistically significant difference in new ICH between anticoagulated patients and those not receiving anticoagulation (4/51 vs. 2/10; $\chi^2 = 0.36$; $p = 0.55$). Only two patients experienced systemic hemorrhage. Out of 42 patients treated with a high-dose heparin regimen, only one patient suffered from hemorrhagic transformation of a venous infarct in a series by Brucker et al. In a smaller series, Wingerchuk et al. closely examined 12 patients with angiographically-confirmed CVT and pre-existing hemorrhagic venous infarction and reported no new ICH in the anticoagulation group and two hemorrhages in those without (33.3%). Neither intracranial nor systemic hemorrhages observed in these studies affected the eventual outcome, usually defined as death or serious physical disability (54–56).

6. Role of endovascular intervention

6.1. Background of endovascular intervention

Endovascular treatment (EVT) is gaining traction as a potential therapeutic option for CVT, where systematic reviews report the frequency of new, post-procedural ICH in between 10% and 17% of cases. (57) The TO-ACT randomized clinical trial recently set out to determine whether EVT in addition to standard medical therapy improved the functional outcomes of patients with CVT. Forty-seven patients (70.1%) enrolled in the trial had prior ICH (22/33 EVT with standard care group vs. 25/34 standard care alone). At the safety endpoint, one patient in the experimental group had a new symptomatic ICH vs. three in the standard care group (3.0 vs. 9.0%, $p = 0.61$). However, six and eight patients in each group, respectively (18.0 vs. 24.0%, $p = 0.59$) developed major hemorrhagic complications, defined as "clinically overt bleeding associated with a decrease in hemoglobin level of 1.9 g/dL, ... required a blood transfusion of 2 or more units, required an operation, or led directly to the death of the patient." These complications were counted as such if the bleeding was retroperitoneal, intracranial, or intraocular, which partially confounds the true rate of ICH (58). As it stands, EVT should not be routinely applied to patients with CVT and is generally reserved for emergency situations. The future of EVTs for CVT is bright, however, as interventionalists become increasingly more experienced operating within the venous system, and novel, more efficient devices for thrombus retrieval are developed.

6.2. role of thrombectomy

Despite the longstanding establishment of anticoagulation as the gold standard treatment in the management of CVT in the acute and chronic stages, various other treatment modalities may be employed concurrently in patients with worsening outcomes, poor prognostic factors, or following a recurrence of CVT in certain patients (42, 54, 59, 60). Although clinical outcomes following CVT are influenced by multiple factors, partial or complete recanalization rates following anticoagulation treatment alone range from 47 to 100% (54, 61–63). It has been proposed that incomplete recanalization or persistent thrombosis in the acute stage may be the mechanism by which further morbidity arises, due to neurologic sequelae such as herniation secondary to mass effect or diffuse cerebral edema (42, 60). It has also been shown that completely and incompletely recanalized patients have similar clinical outcomes, as opposed to those with no recanalization who demonstrated neurologic deficits and/or headaches (61–63). Recanalization most commonly occurs within the first 4 months following CVT, with hyperintensity of the occluded sinus(es) on diffusion-weighted imaging MRI (DWI-MRI) predicting a low rate of vessel recanalization in the following 2–3 months (54, 61, 62). In fact, a prospective study evaluating the use of anticoagulation for CVT and evaluating the relationship between the timing of recanalization and clinical outcome found that early recanalization has no influence on clinical outcome parameters, with 60% of study participants demonstrating recanalization on hospital discharge and an insignificant increase in recanalization rates thereafter (64). Given that anticoagulation alone does not recanalize all patients (referred to as anticoagulation failure) and seeing as certain subgroups of patients demonstrate continued neurological decline due to various neurological sequelae, the utility of endovascular thrombectomy (EVT) for CVT has been widely investigated and documented in the literature, and findings are promising (57, 58, 65–71).

Although virtually all patients afflicted with CVT are treated with anticoagulation, not all patients also require interventions such as EVT. In the ISCVT, the prognosis of CVT was demonstrated to be far better than previously thought, and a clinically identifiable subgroup consisting of 13% of CVT patients was deemed to be at an increased risk of sustaining a bad outcome (54). As such, the ISCVT authors recommended the investigation of more aggressive treatment modalities in patients with co-morbidities or factors that increase the risk of sustaining a bad outcome

(such as mRS $\leq$ 2) (54). Multivariate predictors of death or dependence that increase the risk of sustaining a bad outcome were found to include but are not limited to > 37 years of age [hazard ratio (HR) = 2.0], male sex (*HR* = 1.6), hemorrhage on admission CT scan (*HR* = 1.9), development of coma (*HR* = 2.7), thrombosis affecting the deep cerebral venous system (*HR* = 2.9), infection of the CNS (*HR* = 3.3), mental status disorders (*HR* = 2.0), and cancer (*HR* = 2.9) (4). In the years since the ISCVT was conducted, a myriad of studies has been published that support the utility of EVT as an intervention against CVT (57, 58, 65–71).

A 2022 meta-analysis investigating the safety and efficacy of EVT in patients with severe cerebral venous thrombosis shows that the following symptoms were considered indications for EVT in 33 studies: anticoagulation failure, worsening neurological symptoms, coma, intracerebral hemorrhage, and cerebral edema, and raised intracranial pressure (ICP) (65). These indications for EVT are similar and/or related to many of the negative prognostic indicators illustrated in the ISCVT, which further supports the notion that a subgroup of CVT patients develop a more complex disease that does not respond to anticoagulation alone, in whom EVT may be the best option (54, 65). It has also been demonstrated that mRS $\leq$ 2 equates to a good functional outcome, which was seen in 85% (95% CI: 0.81–0.90) of CVT patients following EVT in the aforementioned meta-analysis (65). Moreover, complete recanalization occurred in 62% (95% CI: 0.53–0.72) of CVT patients following EVT, and partial recanalization occurred in 37% (95% CI: 0.27–0.46) of CVT patients following EVT (65). In all cases, anticoagulation was used prior to thrombectomy, and the follow-up time was 3 months in most of these studies, which is typically a long enough follow-up period, as recanalization continues at insignificant rates thereafter (64, 65). It is important to recall here that the average recanalization rate demonstrated by various studies is around 60% with anticoagulation alone (61–64). At first glance, this value may appear similar to the 62% complete recanalization rate seen in the meta-analysis, however, it is vitally relevant to note that the patients included in the meta-analysis were from studies in which select subgroups of individuals with severe CVT (who were expected to have significantly worse outcomes due to their co-morbidities) were treated with EVT, which makes the comparable outcomes all the more impressive and presumably attributable to treatment effect (61–65).

Given that there are risks associated with EVT for patients with severe CVT, clinicians must balance these risks of receiving treatment with the possibility of poor clinical outcomes for those with severe CVT who fail to respond to anticoagulation. In the meta-analysis assessing the safety and utility of EVT in CVT, complications included new or expanding hematoma following EVT in 4% (95% CI: 0.02–0.05) of patients. Moreover, recurrent CVT occurred in 2% (95% CI: 0.01–0.04) of patients, and catheter-related complications affected 3% (95% CI: 0.01–0.04) of patients (65). In our endeavor to understand the best management of patients with CVT, it is important to note that the clinical severity of the patients assessed in the studies included in the meta-analysis we have referenced was varied, and as such it is difficult to ascertain the external validity of these studies as it relates to suggesting a gold-standard practice. This is especially relevant in CVT patients, as it has been demonstrated that a subset of these patients is predisposed to significantly worse outcomes, making it more challenging to delineate the natural course of the disease from treatment side effects (54).

The Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial is the only randomized controlled trial (RCT) that has been published and evaluates the use of EVT instead of solely standard anticoagulation (58). As the gold standard for better understanding an intervention's utility, one would hope that an RCT would delineate the questions we pose, however, the study was underpowered with 67 total patients enrolled and the trial was halted for futility (58). Moreover, increasing the power of the study may allow us to better discern nuanced differences in treatment outcomes for patients with severe CVT features, such as coma or herniation. These factors are difficult to discern, as CVT is a rare condition and EVT is usually indicated when clinical factors worsen, such as following anticoagulation failure. It would be reasonable to suggest that as anticoagulation failure occurs and time passes, continued thrombosis or clot expansion increases the risks of infarction and/or hemorrhagic transformation, thereby increasing the risk of EVT and potentially decreasing the benefits (59, 60). An RCT with a larger sample size and a greater proportion of severely co-morbid patients may demonstrate greater value to our understanding of this rare condition and its management. In the meantime, it is reasonable to surmise that EVT either has a negligible effect or a positive effect on CVT outcomes in patients with anticoagulation failure and/or declining neurological status and may in fact be demonstrated to impart better outcomes when used as a timely first-line treatment alongside anticoagulation for patients with severe features of CVT. Also, important to note is the variability of endovascular equipment used in all aforementioned studies, which may be of clinical significance, but has thus far not been closely investigated (**Table 2**). Various novel applications of EVT are worthy of being investigated in this population of patients, such as peripheral arterial and/or venous catheters. Although no specific endovascular approach has been specifically established in the treatment of CVT, access is almost always obtained via cranial access catheters. As such, the use of peripheral arterial and/or venous catheters and devices, such as those produced by Inari and Boston Scientific, could inform the application of new devices by extrapolating from vascular cardiology to improve devices we utilize for CVT (72).

7 Role of thrombolysis

Thrombolysis has been investigated in recent years for its applications in CVT, most specifically, for its use as an alternative or adjuvant treatment to EVT (73, 74). In the second largest study (second to ISCVT) investigating treatments of CVT, Wasay et al. illustrate the varying treatments that physicians at multiple centers have elected to use in CVT (73). In their investigation of thrombolysis, they found that 15% of their patient population (n = 182) was treated with non-specific thrombolysis modalities (73). Five percent (n = 10) had pre-thrombolysis hemorrhage, and only 2% (n = 4) demonstrated the development of new post-thrombolysis hemorrhage (73). Moreover, only one patient had a worsening existing hemorrhage (73). Wasay et al. agree with the notions presented in various other studies, including Li et al. who collectively concur that in individuals with severe presentations of CVT, thrombolysis is a reasonable treatment modality, and was said to be preferably used as adjuvant treatment following EVT in select patients (73, 74). Li et al. demonstrated that the use of intra-sinus urokinase is effective for recanalization, with 87% of patients demonstrating complete recanalization, 6% demonstrating partial recanalization, and 8% demonstrating no recanalization (74). They also noted that re-thrombosis occurred, but none occurred following 3–6 months of follow-up, perhaps elucidating a critical window during which complications and re-thrombosis may arise (74).

8 Role of decompressive craniectomy

Overall, CSVT has a good prognosis with anticoagulation as the mainstay of treatment (75–77). However, there is a subset of cases in which CVT is severe with poor outcomes (76, 77). Mortality arises from cerebral edema with subsequent mass effect or intraparenchymal lesions. In the setting of severe CVT, the thrombosis leads to a backup in pressure within the draining veins of the cerebrum. This in turn leads to the breakdown of the blood–brain barrier with subsequent vasogenic edema and elevated ICP. Furthermore, hemorrhagic infarcts can result in a mass lesion causing herniation and increased ICP as well (75). It has been estimated that intracranial hypertension can be present in close to 40% of cases (78). Decompressive craniectomy are proven lifesaving procedures in the setting of malignant intracranial hypertension following arterial ischemic stroke (75, 76). Recent studies and case reports have indicated that not only do decompressive craniectomy impart a survival advantage but can also lead to good outcomes in patients with severe CVT.

Despite a lack of high-quality data regarding decompressive craniectomy in the setting of severe CVT, multiple studies and case series demonstrate the efficacy of procedures in this setting. Decompressive craniectomy have shown both a mortality benefit and good long-term outcomes in severe CVT (75–80). The largest study to date was a retrospective/systematic review conducted by Ferro et al. (76) with a total of 69 patients: 38 from a registry of 22 centers and 31 from a systematic review. Of their patients, there was a mortality rate of 15.9 and 56.5% had what was considered of good outcome. Moreover, the study indicated that decompressive craniectomy for CVT may be of better success than in middle cerebral artery ischemic strokes as their results were superior to three pooled randomized control trials (76). In other studies that have been published,

TABLE 2 | Endovascular treatment devices and adjuvant treatments.

No.	Name	Devices used for EVT	Adjuvant treatment
1	Andersen (2020)	AT, ST, CF, BA	LMWH, LTT
2	Chen (2017)	ST	LMWH, LTT
3	Coutinho et al. (58)	RT, ST	LMWH, LTT
4	Dandapat (2019)	AT, CF, ST	LMWH
5	Dashti (2011)	RT	LMWH
6	Guo (2020)	ST, AT, BA	LMWH, LTT
7	Jankowitz (2012)	AT	LMWH
8	Li et al. (74)	AT	LMWH, LTT
9	Li (2018)	ST	LMWH
10	Liao et al. (68)	AT, ST, CF, BA	LMWH, LTT
11	Ma (2016)	ST	LMWH
12	Medhi et al. (70)	AT	LMWH
13	Mortimer (2013)	CF, BA, AT	LMWH, LTT
14	Mokin (2015)	AT, ST	LTT
15	Qui (2021)	BA	LMWH, LTT
16	Shui (2014)	BA	LMWH
17	Siddiqui (2014)	RT, AT, CT, BA	LMWH, LTT
18	Stam et al. (66)	RT	LMWH, LTT
19	Styczen et al. (69)	AT, ST	LMWH
20	Anand (2020)	BA	LMWH
21	Tsai (2007)	BA	LMWH, LTT
22	Tsang et al. (67)	AT	LMWH, LTT
23	Wang (2020)	ST	LMWH, LTT
24	Zhang (2018)	ST, BA	LTT
25	Zhang (2008)	RT	LTT
26	Zhen (2015)	CF	LMWH, LTT
27	Hongrui (2018)	BA, ST	LMWH
28	Li (2012)	CF	LMWH, LTT
29	Zhang (2018)	BA, ST, CF	LMWH
30	Qiu (2015)	CF, ST	LMWH
31	Shi (2015)	ST	LMWH
32	Yang (2018)	RT, BA, ST	LMWH
33	Zhang (2009)	RT, BA, ST	LMWH

AT, aspiration thrombectomy; BA, balloon angioplasty; CF, catheter fragmentation; CT, coil thrombectomy; CVT, cerebral venous thrombosis; EVT, endovascular thrombectomy; LTT, local thrombolytic therapy; RT, rheolytic thrombectomy; ST, stent retriever thrombectomy; LMWH, low-molecular-weight heparin.

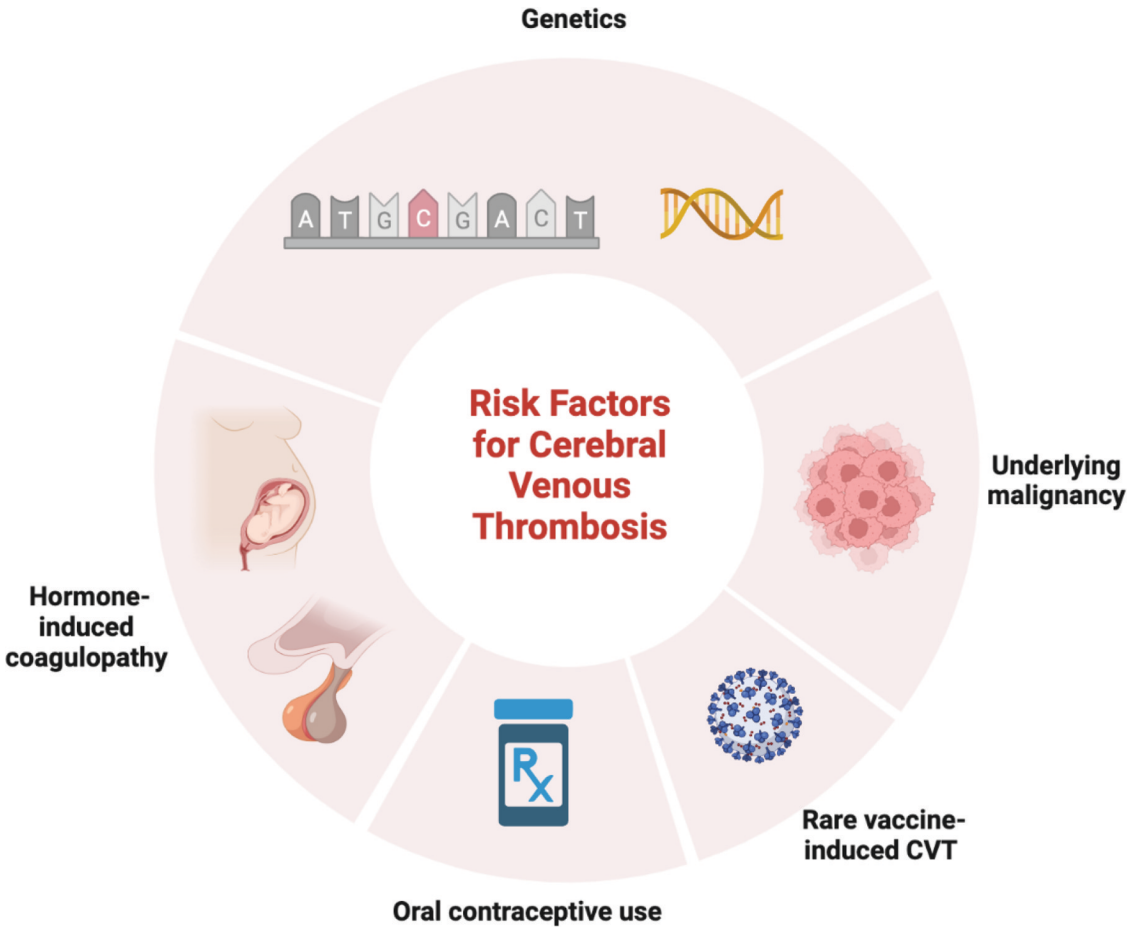

FIGURE 2 | Treatment algorithm for CVT.

good outcomes range from 34.6% in a study by Arauz et al. in 2021 to 76.5% in a study by Rajan et al. in 2012 and 77% by Aaron et al. in 2012 (75, 80, 81). Mortality rates have been reported between 15.9% by Ferro et al. and 42.3% in Arauz et al. with most reported rates landing in the 20–30% range (75–77, 80, 81).

Studies on decompressive craniectomy for malignant CVT have suggested varying prognostic factors for the outcomes following surgery (75–78). Ferro et al. found that blank and blank led to poor outcomes following surgery, while Mahale et al. found that age over 50 years, midline shift > 10 mm, and obliteration of the basal cisterns were prognostic of poor outcome (76, 77). Furthermore, Mahale et al. did not find factors such as clinical deterioration, pupil reactivity, size of the parenchymal lesion, or timing of surgery to be indicative of poor prognosis (77). Unlike Mahale et al., Arauz et al. found only altered mental status to be associated with poor outcome and did not find bilateral parenchymal lesions or age greater than 50 to have a significant effect. Zhang et al. demonstrated that hemorrhage-dominated lesions as well as deep cerebral vein involvement were indicators of poor outcome (78). CVT is a highly pleomorphic disease process with many various presentations which could be the cause of the lack of consensus on prognostic factors (75). Furthermore, studies included varying data points which is why some discrepancy exists. For instance, Ferro et al. did not include midline shift or obliteration of cisterns in their analysis of prognosis (76). Similarly, Arauz et al. did not include cistern status or midline shift (75). Regardless, more studies and data are required to elucidate the best reliable prognostic factors in CVT treated with decompressive craniectomy.

There are no clear guidelines for the indications of decompressive craniectomy, however, different factors have been used and suggested for indications of surgery. The most used indication for surgery is radiologic imaging consistent with impending infratentorial herniation, most commonly the obliteration of the basal cisterns (76, 77, 79, 81). Midline shift was also a common indication for surgical decompression (75, 77). Large intraparenchymal hemorrhages from a hemorrhagic infarct are also considered to indicate surgery, especially when over 6 cm in width (75–77, 80). Other clinical factors that indicate surgery may be warranted are pupillary signs indicative of herniation as well as neurologic status deterioration (76, 77). Arauz et al. operated on patients if they had a decrease in GCS of 4 or more points (75). With respect to surgical decompression, the importance of the timing of surgery is unknown as Aaron

reported a better prognosis in patients undergoing surgery within the first 12 h, whereas Mahale et al. did not find the timing of surgery to be related to outcome (77, 80). Finally, most researchers who reported anticoagulation procedures restarted anticoagulation therapy 48 h after surgery, while Auraz et al. began as early as 24 h after surgery when no contraindications were present (75, 78, 80).

In rare cases, CVT can lead to persistent elevated ICP through both cerebral edema and intraparenchymal lesions. These cases are associated with high mortality and morbidity. Decompressive craniectomy is a suitable treatment option for these patients and has been proven to improve mortality rates and lead to overall good outcomes in patients.

9 Role of shunts

Ventriculoperitoneal (VP) shunts can be used in the treatment of CVT in the presence of hydrocephalus or increased ICP (82, 83). Hydrocephalus is historically not a common sequelae of CVT, however, in a 2015 study by Zuurbier et al., they had an incidence of 20% (73, 84). In patients who do develop hydrocephalus following CVT, the etiology varies and can be either communicating or non-communicating hydrocephalus (82). The more common etiology is a physical blockage of the cerebrospinal fluid (CSF) flow through the third ventricle or foramen of Monro. This arises secondary to hemorrhagic infarction, usually in the basal ganglia or thalamus, or cerebral edema (82, 83). These intraparenchymal lesions lead to hydrocephalus and further increases in ICP necessitating CSF diversion (82, 84). In rare cases, hydrocephalus develops following chronic CVT when no identifiable lesion exists (82). In the setting of chronic CVT, aberrant venous circulation can lead to impaired CSF absorption and subsequent hydrocephalus. This is rare and has only been reported in the literature in a couple of case reports (82, 83). Moreover, it is not understood why this phenomenon is not seen more commonly in chronic CVT (82). VP shunts can also be used for patients who continue to show symptoms of increased ICP following CVT (83). These noted complications are rare, and VP shunts are not commonly employed in treatment. In a 2008 retrospective review by Wasay et al., less than 8% of patients who presented with CVT received a shunt (73). Furthermore, in a 2004 prospective study by Ferro et al., only 1.6% of patients received a shunt (54).

Apart from being an occasional treatment modality for hydrocephalus secondary to CVT, VP shunts have been implicated in the development of CVT (54, 85, 86). Few cases exist in which shunt over drainage and slit ventricle syndrome have led to CVT (85). Furthermore, normal functioning shunts and lumbar punctures have led to thrombosis as well presumably to intracranial hypotension (85–87). The believed mechanism behind the thrombosis reflects on the Monro-Kelly doctrine of intracranial contents (85). When CSF is over-drained, as in the case of slit ventricle syndrome, there is relative hypotension within the cranial vault leading to the engorgement of the venous system. Consequently, the venous blood experiences stasis with an increased risk of thrombus formation (85, 86). This was demonstrated in a report by Almeida et al. in which a 4 year-old patient had shunt over drainage as demonstrated by slit ventricles following VP shunt insertion. He subsequently developed a CVT and a rise in ICP (85). The thrombosis in this patient did not occur when the shunt was first instituted, but rather only once the CSF was over-drained, further giving evidence for the mechanism described above. Similarly, CVT has been described in patients with pseudotumor cerebri following shunt insertion (85, 86). The mechanism is believed to be the same with hypotension leading to venous engorgement. It is also important to note that many patients with pseudotumor cerebri have hypoplastic or stenotic sinuses at baseline further predisposing them to CVT (85, 86). This is demonstrated in Luckett et al. whose patient developed a CVT the day following insertion of a VP shunt (86). However, CVT remains a rare occurrence following VP shunt insertion. Lumbar punctures have also been reported to lead to CVT (85, 87). There have been around 47 cases of this phenomenon reported in total (87). This most likely occurs due to a similar mechanism with a dural tap and syphoning of CSF leading to decreased ICP and subsequent venous engorgement (85, 87). Twenty-seven of these cases were following obstetrical procedures which is associated with a hypercoagulable state at baseline (87). Though rare, CSF diversion, specifically with a VP shunt, has the potential to cause CVT which can lead to significant long-term morbidity and mortality. **Table 2** demonstrates the clinical decision-making that is employed in the management of CVT.

10. Emerging pre-clinical treatments

There is a dearth of pre-clinical models for the management and treatment of CVT. Pre-clinical models of arterial stroke treatments are well established and have guided standards of care in humans, elucidating the benefit of establishing such models for the treatment of CVT (72). One such pre-clinical model for CVT treatment is established by Pasarikovski et al. who demonstrated that residual bridging cortical vein and sinus thrombi may persist despite adequate anticoagulation and recanalization of the sinuses on imaging in animal models (Yorkshire swine), to which the authors attribute the poor outcomes of patients with severe CVT (72). As such, they recommend the use of thrombolysis to dissolve the remaining clot (72). This model and others that endeavor to translate various devices such as peripheral arterial and/or venous access devices and catheters may be integral to the development of effective treatment modalities in the management of CVT.

11. Conclusion

In the management of CVT, clinicians are tasked with the challenge of achieving favorable outcomes in a rare pathological state that is understudied. In this review, we elucidate the various etiologies that facilitate the development of CVT, including genetic risk factors such as MTHFR polymorphisms, Factor V Leiden mutations, and prothrombin mutations. Moreover, hormonal dysregulation from oral contraceptive use, pregnancy, and even topical hormone medication use has been implicated in producing a state of fibrinogen over expression and coagulation factor dysregulation, resulting in a pro-thrombotic state. Malignancy and infection, from sepsis to COVID-19, which are known pro-thrombotic states, are also implicated in the pathogenesis of certain cases of CVT.

The diagnosis of CVT is often suspected due to hyperdensity of the cerebral sinus(es) on non-contrast CT, and imaging that is unequivocal is often made more accurate through the use of CT and MR venography, with digital subtraction angiography used in cases that are still inconclusive. Once a diagnosis is made, treatment is initiated with LMWH anticoagulation or the use of unfractionated heparin in patients with renal insufficiency. DOACs have been used more recently in the management of CVT with promising efficacy.

As CVT develops, clinicians must act promptly to reduce the risks of sequelae, such as stroke, mass effect and herniation, hemorrhagic conversion, and/or the development of obstructive hydrocephalus. Following treatment failure of anticoagulation, studies have demonstrated the efficacy of thrombectomy with or without the use of intrasinus urokinase thrombolysis in cases of severe or recurrent CVT. Open decompressive hemicraniectomy and shunting can be utilized to manage the sequelae of CVT, such as mass effect/herniation and obstructive hydrocephalus development, respectively. The thrombectomy techniques and devices utilized in CVT are still being fine-tuned, and RCTs assessing the efficacy of various approaches and devices are lacking in the literature. RCTs with higher power investigating the efficacy of thrombectomy against thrombectomy with thrombolysis are warranted, as are studies investigating the use of repurposed peripheral venous and/or arterial catheters and devices. As pre-clinical models of CVT management are further developed, we can hope to develop a better understanding of the nuances of CVT treatment modalities.

Author contributions

AK and BL-W: conceptualization. AK and MM: planning of manuscript content. AK, MM, and RM: literature assessment. AK, MM, RM, and ML: writing of the manuscript. AK, MM, RM, ML, and BL-W: approval of the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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