Cerebral venous thrombosis: Diagnosis and management in the emergency department setting

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**Abstract**

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**Introduction:** Cerebral venous thrombosis (CVT) is an uncommon neurologic emergency associated with significant morbidity and mortality that can be difficult to differentiate from other conditions. It is important for the emergency clinician to be familiar with this disease as it requires a high index of suspicion, and early diagnosis and management can lead to improved outcomes.

**Objective:** This narrative review provides an evidence-based update concerning the presentation, evaluation, and management of CVT for the emergency clinician.

**Discussion:** CVT is due to thrombosis of the cerebral veins resulting in obstruction of venous outflow and increased intracranial pressure. Early recognition is important but difficult as the clinical presentation can mimic more common disease patterns. The most common patient population affected includes women under the age of 50. Risk factors for CVT include pregnancy, medications (oral contraceptives), inherited thrombophilia, prior venous thromboembolic event, malignancy, recent infection, and neurosurgery. CVT can present in a variety of ways, but the most common symptom is headache, followed by focal neurologic deficit, seizure, and altered mental status. Imaging studies such as computed tomography (CT) venography or magnetic resonance (MR) venography should be obtained in patients with concern for CVT, as non-contrast CT will be normal or have non-specific findings in most patients. Treatment includes anticoagulation, treating seizures and elevated ICP aggressively, and neurosurgical or interventional radiology consultation in select cases.

**Conclusions:** CVT can be a challenging diagnosis. Knowledge of the risk factors, patient presentation, evaluation, and management can assist emergency clinicians.

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1. Introduction

Cerebral venous thrombosis (CVT) is an uncommon neurologic emergency that can lead to stroke, seizures, and death. CVT is defined by thrombosis of the intracranial veins and dural sinuses and has an estimated annual incidence of 0.3–1.5 cases/100,000 person-years, accounting for up to 1% of all strokes worldwide [1–3]. The disease is difficult to differentiate from other more common neurologic conditions due to its varied presentations. Delays in diagnosis are associated with higher morbidity, however, prompt recognition, diagnosis, and management can lead to improved outcomes [4]. Thus, it is important for the emergency clinician to be familiar with this disease.

2. Methods

This narrative review provides a focused overview of CVT for emergency clinicians. The authors searched PubMed for English language articles from 1990 to November 2020 using the keyword and Medical Subject Heading “cerebral venous thrombosis” for production of this narrative review, restricting results to retrospective and prospective studies, systematic reviews and meta-analyses, narrative reviews, and clinical guidelines. Initial literature search revealed 486 full text articles. Article inclusion was determined by author review and consensus based on clinical relevance to emergency department (ED) evaluation and management. When available, retrospective and prospective studies, systematic reviews/meta-analyses, and clinical guidelines were preferentially selected. A total of 57 articles were determined to be of relevance to emergency clinicians by author consensus and included in this narrative review. Of the 57 articles included in this review, there were 5 systematic reviews/meta-analyses, 2 guidelines from clinical societies, 7 RCTs, 24 observational studies, and 19 clinical reviews. Authors did not pool data for meta-analysis, as this is a narrative review.
3. Discussion

3.1. Pathophysiology

The cerebral veins drain the capillary network that supplies the brain with blood (Fig. 1). The dural sinuses also drain the cerebrospinal fluid (CSF) via the arachnoid granulations and return the CSF into circulation through the bloodstream [5]. An obstruction within this drainage system leads to increased venous pressure and reduced capillary perfusion pressure, which can result in ischemia, edema, elevated intracranial pressure (ICP), and even hemorrhagic infarction [1, 5]. Two types of edema result from CVT: vasogenic and cytotoxic edema [6]. Vasogenic edema results from the elevated venous pressure that leads to disruption of the blood brain barrier and blood leakage across the interstitial membrane [6, 7]. If the venous pressure remains elevated, subsequent ischemia of cerebral tissue disrupts oxygen-dependent biochemical pathways and leads to cytotoxic edema [6, 7]. Compression of the nerve fibers within the veins is thought to cause headache [5].

Fig. 1. Cerebral Venous Anatomy. Image Courtesy of Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Major_venous_sinuses_and_their_tributaries.png

3.2. Epidemiology

Several multicenter cohort studies suggest a female predominance to CVT [8-10]. The International Study on Cerebral Venous Thrombosis (ISCVT), published in 2004, reported 74.5% of patients with CVT were women [9]. Additionally, this study found that 78% of patients with CVT were less than 50 years old [9]. A more recent cohort study of CVT among a Norwegian population found an equal prevalence of CVT among the sexes [11]. Approximately 85% of patients with CVT have at least one identifiable risk factor for thrombosis (Table 1) [12, 13]. Oral contraceptive pill (OCP) use, pregnancy/peripartum status, obesity, and hypercoagulability are several of the most common risk factors, with OCPs increasing the risk of CVT six-fold [12, 14]. Other risk factors include inflammatory conditions such as vasculitis or connective tissue disorders, sickle cell disease, head trauma, nephrotic syndrome, and dehydration [3, 14]. Local infections of the head and neck, such as mastoiditis and sinusitis, have been reported to be associated with CVT, present in 8.2% of cases in one study [15]. Another important potential risk factor is recent surgery, particularly neurosurgery, which has been associated with up to 2% of CVT cases [9, 12]. Malignancy has been reported to be associated with CVT in approximately 5% of cases, although some studies have noted that malignancy is a more common cause of CVT in patients over age 55, present in 25% of cases [15, 16].

3.3. History and examination

History should focus on the presence of these risk factors and medications that increase risk of thrombosis. In a study of risk factors for CVT, smoking, hypertension, and diabetes did not reach statistical significance, possibly reflecting the younger age of the population most affected by CVT [12]. Thus, the emergency clinician should consider CVT in patients with stroke-like symptoms without traditional stroke risk factors [12]. One study estimated OCP use among 54–71% of female patients with CVT, while another found OCP use in 10–73% of female patients with CVT [2, 3, 8, 12]. Pregnancy and the first 6 weeks postpartum are higher risk periods for the development of CVT. One study estimated an odds ratio (OR) of 17.24 for pregnancy/post-partum period for CVT [12]. OCP use can also be easily missed if a thorough medication review is not performed. Additional risk factors identified for CVT include glucocorticoid use (OR 18.26; 95% CI 3.25–102.55), antiphospholipid syndrome (OR 6.98; 95% CI 2.06–23.6), factor V Leiden (OR 2.51; 95% CI 1.93–3.27), prothrombin 20210A (OR 5.53; 95% CI 3.98–7.89), and protein C deficiency (OR 7.69; 95% CI 5.16–11.96) [12]. One small study found a higher risk of CVT among patients at high-altitude, although many of these patients already had one hypercoagulable risk factor [17]. Patients present along a clinical spectrum based on the location of the thrombus, severity of ICP elevation, and presence of edema, making diagnosis difficult. Headache is the most common presenting complaint of CVT, occurring in 81–95% of patients, and focal neurologic deficits, seizures, and altered mental status can be other presenting features of CVT (Table 2) [2, 8, 11, 17, 18]. However, over 5% of patients will present without headache [18]. While headache is common in ED patients, several distinguishing factors may suggest CVT, as well as other diseases (Table 3). Additionally, while neurologic abnormalities are often utilized as a trigger for additional evaluation in patients presenting with headache, the VENOST study found that 25% of cases of CVT presented as isolated headache [8]. Unlike with subarachnoid hemorrhage, the headache in CVT tends to be more subacute, rather than sudden in
onset [3,8,18]. One study found that 57% of patients presented with sub-acute or chronic headaches, with symptoms progressing from 4 days to greater than 2 weeks, leaving 43% presenting acutely [8]. Another study reported 60% of patients presented acutely, although this study defined acute as 1–4 days after symptom onset [3]. While rare, there have been case reports of CVT presenting as maximal in onset, “thunderclap” headache, which could prove problematic as clinicians may anchor on evaluating for subarachnoid hemorrhage [3].

Headache that is worsened with maneuvers that increase ICP (i.e., Valsalva maneuver, bending over, etc.) can be suggestive of CVT [3]. However, this is a non-specific finding and is common in other diseases that present with headache and increased ICP [3]. The location of headache in CVT is variable given the various locations for CVT as well as associated symptoms [3]. However, most cases of CVT involve multiple locations and therefore may not present as a clear syndrome [15]. A summary of the frequency of different locations for CVT as well as associated symptoms is presented in Table 4.

### 3.4. Evaluation

#### 3.4.1. Laboratory testing

Laboratory evaluation cannot be used to rule in or rule out CVT. D-dimer is often elevated in patients with CVT, but literature demonstrates a sensitivity of 82–94% [1–3,18]. The sensitivity is highest in patients with acute, extensive disease and lower in those with subacute or more focal thrombus. A recent prospective multicenter study proposed a predictive clinical score for the diagnosis of CVT (Table 5) [30]. The score ranges from 0 to 14 points (17 points if D-dimer is utilized). Low risk is 0–2 points, moderate risk is 3–5 points, and high risk is ≥6 points. D-dimer is not a mandatory part of the score but can be incorporated (D-dimer ≥500 μg/L is 3 points). The authors found that among the 186 patients with low probability for CVT (score 0–2), 11 patients, or 5.9%, were ultimately diagnosed with CVT [30]. Among this group of 11 patients who were low probability but diagnosed with CVT, all had a D-dimer ≥500 μg/L [30]. In this study the best CVT prediction model resulted from a CVT clinical score ≥6 and D-dimer ≥500 μg/L, with a sensitivity of 83% and specificity of 86.8% [30]. Although this is a promising step towards development of a useful tool for ruling out CVT, further studies are required [30]. Additionally, due to the poor specificity of D-
Concerning for CVT include the increased opening pressure, pleocytosis, and increased red blood cells not definitively indicated for all patients with suspected CVT [7]. A study of LP in CVT patients found that LP was normal in 44% of patients with CVT [31]. This study also found that the performance of an LP did not affect the prognosis of patients with CVT [31]. However, particularly among acutely ill patients, LP can play an important role in evaluating for life-threatening diagnoses like bacterial meningitis or subarachnoid hemorrhage.

3.4.2. Imaging

CVT is primarily diagnosed by imaging [13,19,32]. The most common initial imaging modality obtained in the ED in patients with a suspected neurological condition (e.g., high-risk headaches, stroke, intracerebral hemorrhage, etc.) is non-contrast head computed tomography (CT). Non-contrast head CT possesses an important role in evaluating for other dangerous conditions such as intracerebral hemorrhage. However, this test has poor sensitivity and can be normal in 30–60% of patients with CVT [7,18]. Non-contrast head CT findings concerning for CVT include the “dense triangle sign” (thrombosis in the superior sagittal sinus) and the “cord sign” (thrombosis of cortical or deep veins) [3,7]. The cord sign is an area of increased attenuation in a dural sinus or vein (Fig. 2). This finding represents a clot, which appears hyper-attenuated in the acute phase, typically when symptoms have been present for less than one week. However, the clot will become iso- or hypo attenuated in the subacute and chronic phases [6,33]. Additionally, dehydration and elevated hematocrit may cause a false cord sign [34]. This sign may be found in 6.7–64.6% of cases [33–36]. Overall, the majority of non-contrast head CTs in CVT will be normal or have nonspecific signs of increased ICP, parenchymal abnormalities, or infarctions in multiple arterial distributions [2,3,7,18]. Thus, a normal non-contrast head CT should not be used to exclude the diagnosis of CVT, and in patients with severe headache or other findings concerning for CVT, further evaluation is necessary [32]. Hemorrhage may be present in approximately one third of patients, which is more commonly parenchymal and may occur in several arterial regions [32,34]. Head CT with intravenous (IV) contrast may reveal the “empty delta sign” (non-opacified thrombus surrounded by the collateral veins of the sinus wall after injection of contrast), which is consistent with a diagnosis of CVT but is present in only 29–35% of cases [6,34,37]. The empty delta sign may not be present in the acute phase, due to the hyperattenuated thrombus, but it may be present in the subacute phase [6].

CT or magnetic resonance imaging (MRI) with venous phase imaging is the recommended diagnostic modality and has high sensitivity and specificity. CT venography sensitivity and specificity approximate 95% for diagnosis of CVT and is readily available in most EDs [7,35]. MRI (without venous phase imaging) findings are dependent on the age of thrombus [6,7,38]. In the acute phase, 0–15 days after symptom onset, the thrombus will be predominately isointense on T1 weighted images and hypointense on T2-weighted images, resulting in the potential for missed diagnosis if MRI without venous phase imaging is used [6,34]. In the subacute phase, or days 6–15, the thrombus will be hyperintense on both T1 and T2 weighted images, thus making diagnosis easier radiographically [6,34]. After 15 days the thrombus can be isointense on T1 and T2 weighted images, again increasing the risk for missed diagnosis [6,34]. Because the duration of the CVT impacts MRI test characteristics, venous phase imaging is necessary. Similar to CT venography, magnetic resonance venography (MRV) displays high sensitivity and specificity for diagnosis [7,35]. While CT venography and MRV likely

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency (%)</th>
<th>Associated symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Sagittal Sinus</td>
<td>62–71</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemisensory loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemiparesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td>Lateral Sinuses</td>
<td>31–47</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aphasia (left sided)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mastoid pain</td>
</tr>
<tr>
<td>Straight Sinus including the Deep</td>
<td>10–18</td>
<td>Altered Mental Status</td>
</tr>
<tr>
<td>Venous System</td>
<td></td>
<td>Gaze palsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eye pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proptosis</td>
</tr>
<tr>
<td>Cavernous Sinus</td>
<td>1–4</td>
<td>Cranial nerve III, IV, VI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>palsy</td>
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</tbody>
</table>

Table 4

Frequency and Associated Symptoms of Various Locations of CVT [9,10,15].

<table>
<thead>
<tr>
<th>Component</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure(s) at presentation</td>
<td>4</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>4</td>
</tr>
<tr>
<td>Oral contraception</td>
<td>2</td>
</tr>
<tr>
<td>Duration of symptoms &gt;6 days</td>
<td>2</td>
</tr>
<tr>
<td>Worst headache ever</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic deficit at presentation</td>
<td>1</td>
</tr>
<tr>
<td>D-Dimer ≥500 μg/L</td>
<td>3</td>
</tr>
</tbody>
</table>

Interpretation: Low risk – 0–2, Moderate risk – 3–5, High risk – greater than 6. * D-dimer is not a mandatory part of the score, but if obtained, a D-dimer ≥500 μg/L is 3 points.

3.4.3 CVT Clinical Score

<table>
<thead>
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<th>Component</th>
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</tbody>
</table>

Fig. 2. Cord Sign on non-contrast head CT. Image Courtesy of Wikimedia Commons: https://commons.wikimedia.org/wiki/File:Duralvenoussinusthrombosis.png
perform similarly, MRV may be more effective for diagnosis in those with evidence of deep vein involvement (i.e., altered mental status).

3.5. Management

The overall goals of treatment of CVT are to treat the sequelae of CVT, prevent propagation of the clot, recanalize the occluded vessel, and prevent thrombosis elsewhere in the body.

3.5.1. Seizures

Important sequelae of CVT include seizures and increased ICP. Seizure is an independent prognostic risk factor for mortality [39]. Patients actively seizing should be treated with benzodiazepines. A retrospective study of seizures in CVT reported that lorazepam was the most commonly used medication to treat acute seizures from CVT [40]. Seizures in CVT are associated with supratentorial lesions [40]. European guidelines make a weak recommendation for patients with CVT who present with seizures and a supratentorial lesion to be started on an anti-epileptic drug to prevent early recurrent seizures, but they make no specific recommendation on agent choice or duration [16]. Seizure prophylaxis for all patients with CVT is not recommended.

3.5.2. ICP

Elevated ICP can be a devastating consequence of CVT. A major cause of death from CVT for patients is transtentorial herniation; thus, early management of ICP is critical [39]. There is little evidence to guide treatment of increased ICP in the setting of CVT. Therapeutic LP can be considered to reduce ICP, and although no randomized studies have demonstrated therapeutic benefit in CVT, studies have shown that LP is safe in patients with CVT who have isolated intracranial hypertension. LP is contraindicated in those with large lesions at risk for herniation [14,31]. Performing the LP must be balanced with the need for anticoagulation. European guidelines do not recommend acetazolamide as it has only been evaluated in small non-randomized studies with no clear benefit [16,41]. Steroids have not been shown to be beneficial, with one case-control study showing no difference in rates of death or dependence when compared with control [42]. They may be beneficial in those with an underlying inflammatory disorders such as systemic lupus erythematosus [16]. Although the most recent European Stroke Organization guidelines from 2017 did not comment on these strategies, older guidelines from the European Federation of Neurological Societies in 2010 recommended elevating the head of bed to 30 degrees, hyperventilation to 30–35 mmHg PaCO₂, and either hypertonic saline or mannitol to lower ICP based on expert opinion [16,43]. Emergent neuropsychiatric consultation is recommended in patients with CVT and signs of impending herniation, as small case series and observational data have shown that decompressive surgery can be life-saving, but there are little data to guide patient selection [44].

3.5.3. Anticoagulation

Anticoagulation is the mainstay of ED treatment of CVT with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) to recanalize the occluded vein, prevent thrombus propagation, and treat the underlying prothrombotic state [45]. Intracerebral hemorrhage is not a contraindication to starting anticoagulation. Of the RCTs included in a Cochrane review evaluating anticoagulation for CVT, 25%–49% of patients had intracerebral hemorrhage prior to starting anticoagulation, and no patients developed new intracerebral hemorrhage (95% CI 0%–9%) [45]. It should be noted that RCTs of anticoagulation in CVT excluded patients with end stage renal disease, liver disease with evidence of synthetic dysfunction, recent gastrointestinal bleed, thrombocytopenia, and hypertension with a diastolic pressure greater than 110 mmHg [40]. LMWH may be more effective than UFH, unless the patient is clinically unstable or invasive intervention is planned. One RCT of 66 patients found LMWH reduced mortality (0% with LMWH) compared to UFH (19% mortality), as well as increased likelihood of complete recovery (88% LMWH versus 63% UFH) [47]. A case-control study found greater independence with LMWH versus UFH (92% versus 84%, OR 2.4) [48]. Warfarin or direct oral anticoagulants (DOACs) can be used for long term anticoagulation in CVT [49–51]. A meta-analysis including 6 studies published in 2020 found DOACs were as effective as warfarin in thrombus recanalization and functional outcomes [52]. Of note, in studies evaluating warfarin or DOACs for patients with CVT, LMWH was the initial anticoagulation agent [52]. Decisions concerning the long-term anticoagulation agent and duration of anticoagulation requires consideration of underlying thrombotic risk factors and should be made in conjunction with a specialist in neurology or hematology. The European guidelines recommend a period of 3 to 12 months [16]. The use of systemic thrombolysis has been described, but a systematic review found a risk of serious bleed of 11.5% and a risk of death of 7.7% with systemic thrombolysis. European guidelines currently do not recommend systemic thrombolytics [16,53]. The role of endovascular therapy for CVT has previously been complicated by the non-randomized nature of studies on endovascular therapy, with patients in the intervention group more critically ill [41,54]. However, a recent RCT of endovascular therapy showed no difference in mortality or modified Rankin Score (mRS) of 0–1 when compared with standard of care [55]. In this study, over 80% of patients in both groups had a mRS of 0–2 at discharge, considered a good outcome in most of the ischemic stroke literature, reflecting the overall good prognosis for the disease. However, a subset of patients with CVT may benefit from endovascular therapy, and thus the decision to intervene should be made in conjunction with neurology, neurosurgery, and interventional radiology if endovascular therapy is available [55]. Although overall the prognosis for CVT is favorable, there are potentially devastating consequences to this disease [56]. Clinically stable patients should be admitted for initiation of anticoagulation and neurology and hematological consultation. Patients with evidence of neurologic deterioration or those requiring neurosurgical or interventional radiology procedures should be admitted to an intensive care setting.

3.6. Prognosis

Patients with diagnosed CVT should be admitted for further evaluation of the underlying etiology. Mortality approximates 5%, with risk of permanent disability reaching 20%. The most important factors associated with poor prognosis include malignancy (OR 4.53), coma (OR 4.19), thrombosis of the deep venous system (OR 3.03), any mental status disturbance (OR 2.18), male gender (OR 1.60), and intracerebral hemorrhage (OR 1.42). In the absence of these factors, prognosis is favorable [16,57].

4. Conclusions

CVT is an uncommon cause of headache and stroke that primarily occurs in patients less than 50 years. Women are more commonly affected than men. Thrombus within the cerebral veins can cause increased ICP, cerebral edema, and ischemia. Patients may experience seizures, stroke, and altered mental status, leading to herniation and death. Early recognition is important but difficult as the clinical presentation can mimic more common disease patterns. Imaging studies such as CT venography or MRV should be obtained. Laboratory tests are unlikely to assist in these patients, though D-dimer has been investigated. Treatment includes anticoagulation. Seizures should be treated aggressively. Evidence of herniation requires emergent stabilization with lowering of ICP and emergent neurosurgical consultation.

Declaration of Competing Interest

No conflicts for any author.
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