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Abstract Cerebral venous thrombosis (CVT) is an uncommon cause of stroke with the incidence of 0.5 % from all strokes. The clinical presentation with cerebral hemorrhage constitutes a diagnostic challenge. Approximately one-third of CVT patients developed intracerebral hemorrhage (ICH). Associated factors include older age, female sex, acute onset (48 h), headache, decreased level of consciousness, seizure, elevated blood pressure and papilledema. MRI and MR venogram is the most recommend diagnostic modality in CVT. Anticoagulation therapy is the most commonly accepted treatment even in patients with ICH related CVT. Mechanical thrombectomy/thrombolysis may be considered in patients with neurological deterioration despite intensive medical treatment. Intracerebral hemorrhage in the context of CVT is usually associated with poorer outcomes compared to CVT without ICH.

Keywords Cerebral hemorrhage · Cerebral hematoma · Venous infarct · Hemorrhagic · Subarachnoid hemorrhage · Cerebral venous thrombosis · Sinus thrombosis · Stroke · Disease management · Anticoagulation or oral anticoagulants · Heparin · Thrombolysis/thrombectomy

Introduction

Cerebral venous thrombosis (CVT) is the occlusion/thrombosis of the veins and/or venous sinuses in the brain. CVT is an uncommon cause of stroke. CVT was first described by Dr. Ribes, French physician in 1825 [1], who reported a 45-year-old man presented with severe headaches, epilepsy and delirium. The incidence of CVT accounts for 3–5 cases per 1 million population or 0.5 % of all strokes [2, 3]. Among patients with CVT, the incidence of cerebral hemorrhage is about 35 % to 39 % [4, 5]. The advent of novel investigations including CT and MRI brain facilitate the clinical diagnosis of CVT. Cerebral venous sinus thrombosis most commonly affects young adults, predominantly in women [4–7] with various clinical presentations, most commonly persistent headaches accompanied by focal neurological deficit or seizures. However, the presentation with cerebral hemorrhage may be challenging and a common pitfall in diagnosing cerebral venous sinus thrombosis. In addition, cerebral hemorrhage in CVT is a prognostic factor, usually associated with poorer outcomes [5, 7, 8]. This review summarizes the pathogenesis, risk factors, clinical presentations, neuroimaging, and treatment of cerebral hemorrhage in CVT.

Pathogenesis

The pathogenesis of CVT is composed of two mechanisms. First, thrombosis of the cerebral veins, which may cause focal neurological symptoms. Second, thrombosis of the major sinuses, which may contribute to intracranial hypertension due to progressive and persistent venous congestion. These two processes may occur simultaneously [2]. The thrombosis of cerebral veins causes ischemic neuronal damage, venous infarction, and petechial hemorrhage then becoming a large hematoma, perpetuating the cerebral edema.
The cerebrospinal fluid produced from ependymal cells in choroids plexus and then circulates from the ventricle to the subarachnoid space, to the arachnoid villi and consequently drains into the superior sagittal sinus. As a result, the thrombosis of the major sinuses compromises the cerebrospinal fluid absorption resulting in the development of intracranial hypertension [2, 9].

**Risk Factors**

There are several established risk factors for CVT. They can be divided in two categories: inherited thrombophilia (e.g. antiphospholipid) and acquired (Transient or persistent) prothrombotic states including trauma, cancer, infection, surgery, pregnancy, puerperium, exogenous hormones, antiphospholipid syndrome (frequently inherit) [9••]. In a study including 220 CVT patients, the authors compared risk factors between non-hemorrhagic and hemorrhagic CVT. They found that age, sex, high blood pressure at admission, hemorrhagic lesions, multiple sinus involvement and sinus-vein thrombosis were associated with hemorrhagic CVT [10•]. Pregnancy and puerperium were reported to be an independent risk factor in hemorrhagic CVT [10•]. Other studies, found no association between puerperium and cerebral hemorrhage among patients with CVT [11]. Acquired thrombophilia was predominantly found in hemorrhagic compared with non-hemorrhagic CVT (22 % and 12 %; \(p<0.0001\)) [11].

**Clinical Manifestations**

Cerebral venous sinus thrombosis has several clinical presentations. Most commonly, it can be classified into 4 groups, including: i) isolated intracranial hypertension (patients may present with headache, diplopia, visual impairment (severe papilledema), decreased level of consciousness, or sixth nerve palsy, ii) focal syndrome (e.g. motor weakness, sensory deficit, aphasia, seizure, iii) encephalopathy, and iv) cavernous sinus thrombosis (orbital pain, chemosis, proptosis and oculomotor palsies) [2, 3]. Isolated intracranial hypertension was reported in 20–23 % [5, 6] and can be found in association with other symptoms [3].

In the largest multicenter studies of CVT, cerebral hemorrhage was reported in 35–39 % [4, 5]. The clinical manifestations of cerebral hemorrhage in CVT patients mostly presented with older age, females, with acute onset (48 h) 47 % [11]. Headache, mental status disorder, confusion, coma, loss of consciousness, aphasia and seizure, high blood pressure, papilledema were commonly found in hemorrhagic CVT patients [10•, 11]. Other studies found no association between headache and the presence of hemorrhage on CT or MRI brain \(p=0.1\) [12]. Additional clinical manifestations including cranial nerve palsy, motor and sensory deficit, dysarthria or ataxia were also reported [10•]. The clinical manifestations are summarized in Table 1.

Some authors classified intracranial bleeding in patients with CVT as intraparenchymal hematoma (12 %) and hemorrhagic infarction (20 %) [10•]. In cerebral hemorrhage from CVT, supratentorial hemorrhage was found in 43 % whereas infratentorial hemorrhage was reported in 1.6 % [5]. Subarachnoid hemorrhage (SAH), subdural hematoma and peri-callosum hemorrhage are uncommon presentations of CVT [13–21].

In the largest study of CVT, SAH was found in 5 (<1 %) patients. In a case series including 26 patients with subarachnoid haemorrhage (SAH) due to CVT, thundereclap headache was reported in 62 %, nuchal rigidity 35 %, seizure 35 %, hemiparesis 35 %, alteration of consciousness in 27 % and speech impairment 19 % [13]. Interestingly, the location of SAH mostly involved cerebral convexity and spares the basal cisterns and skull base [13]. Most common location of venous thrombosis included the transverse sinus, the sigmoid sinus, and concomitant sinus and vein thrombosis [10•, 11].

**Diagnosis**

In the past two decades, advanced brain imaging had a significant role in improving the diagnosis of CVT. CT brain, CT venogram (CTV), MRI brain, MR venogram (MRV) and conventional angiogram are the common investigations used in the diagnosis of CVT.

**Computed Tomography**

CT brain is usually the initial screening imaging in patients with an acute neurologic deficit. In non-contrast CT brain, spontaneous density ("dense cord sign"), represents thrombosed cortical vein or sinus (Fig. 1). In contrast CT brain, the delta sign represents thrombosis of the posterior portion of the superior sagittal sinus (SSS). However, only one third of CVT cases presented the direct sign [22]. Similar findings can be observed when other sinuses are involved.

Bilateral cerebral hemorrhage, multifocal hemorrhage, hemorrhagic infarction, or an infarction outside the boundaries for an arterial territory should be suspicious for cerebral venous sinus thrombosis [23].

**CT Venography**

CT venography (CTV) is a diagnostic tool to initially assess patients with a presumed diagnosis of CVT [23]. CTV is
usually more available specially in non-stroke centers, hav-
ing the advantage of rapid access specially in patients with con-
traindications for MRI study. Both the American Heart
Association (AHA) [9••] and the European Federation of
Neurological Societies (EFNS) guidelines [24••] consider
MRI as the preferred imaging choice and CTV as an
screening tool when MRI isn’t available. Limitations of
CT scan includes the exposition to iodinated contrast and
ionizing radiation, bone artifact with the adjacent dural
sinus, allergy of iodine contrast and impairment of renal
function. Together these are relevant considerations when
follow-up examinations are required [24••]. The

| Table 1 | Demographic features and clinical manifestations |
|-------------------|-------------------|-------------------|
| | Girot et al. [11] Total N=624 | Kumral et al. [10•] Total N=220 |
| | ICH* N=245 | ICH* N=26 | HP* N=45 |
| Age (range) | 40(16–82) | 54(35–75) | 46(26–62) |
| Female | 189(76) | 16(61.5) | 39(86.7) |
| Mode of onset | | | |
| Acute (48 h) | 114(47) | NR | NR |
| Subacute (48 h to 30 days) | 117(48) | NR | NR |
| Chronic (>30 days) | 13(5) | NR | NR |
| Headache | NR | 25(96) | 45(100) |
| Confusion/drowsiness | NR | 4(15) | 5(11) |
| Coma | NR | 7(27) | 9(20) |
| Loss of consciousness | NR | 7(27) | 9(20) |
| Behavioral findings | 76(31) | 15(58) | 24(53) |
| Seizure | 135(55) | 11(42) | 23(51) |
| Aphasia | 88(36) | 9(35) | 10(22) |
| Diplopia | NR | 9(35) | 6(13) |
| Dysarthria | NR | 10(39) | 20(44) |
| High blood pressure | NR | 4(15) | 10(22) |
| GCS<9 | 22(9) | NR | NR |
| Papilledema | NR | 10(39) | 9(20) |
| Cranial nerve palsy | NR | 11(46) | 10(22) |
| Motor deficits | 123(50) | 12(35) | 15(33) |
| Sensory deficit | NR | 9(35) | 16(36) |
| Ataxia | NR | 8(31) | 12(27) |

Number in bracket represent percentage
NR not reported; * Intracranial hemorrhage; ª Hemorrhagic infarct

Fig. 1 A 42-year-old woman presented with left side headache, confusion, and decrease level of consciousness; a Non-contrast CT brain axial image showed left temporal hemorrhage. b Noncontrat CT brain axial image showed thrombosis left transverse sinus (arrow)
development of haemorrhage due to CVT mostly occurs with the thrombosis of large sinuses e.g. superior sagittal sinus, transverse sinus, sigmoid sinus (Fig. 2), multiple sinuses and/or concomitant sinus-veins thrombosis [10, 11].

**Magnetic Resonance Imaging**

MRI and MR Venogram brain is a non-invasive and most recommended imaging modality for the diagnosis of CVT [9, 24] MRI is more sensitive in detection of CVT every stage after thrombosis including patients who suspected CVT in normal CTV [9, 26]. Visualized thrombus in T1-weighted images of MRI brain or loss of signal in the venous system from MRV are key elements to confirm the diagnosis. The thrombus itself may be difficult to visualize in the acute phase (first 5 days) because the thrombus is isointense compared with the brain tissue on T1-weighted images and hypointense on T2-weighted images. In the subacute stage (5–15 days), the thrombus is hyperintense on T1-weighted and subsequently on T2-weighted. After 15 days, the thrombus will become homogeneous and decrease in signal intensity of all image sequences [23, 25, 26]. MRI brain demonstrates bilateral cerebral hemorrhage, multifocal hemorrhage or hemorrhagic infarction, which is unusual for arterial territory and should be suspicious for cerebral venous sinus thrombosis [23]. The brain parenchyma abnormality may help identify the site of venous sinus thrombosis for example, frontal, parietal or occipital lobe involvement suggest superior sagittal sinus thrombosis, temporal lobe parenchyma changes may suggest lateral (transverse) and sigmoid sinus thrombosis, and deep parenchymal changes (e.g. thalamic haemorrhage) would suggest thrombosis of the [internal cerebral vein], vein of Galen or straight sinus [9]. However, the limitation of a MRV brain is flow artifacts that can lead to false diagnosis due to the anatomic variability of the venous system [25, 26]. Contrast enhanced MRV is more sensitive than time-of-flight MRV in demonstrate of the thrombus and small vein [26].

**Conventional Angiographic**

Conventional angiographic, an invasive procedure, can be used in selected situations when MRI/MRV is not available and there is a high level of suspicion. It carries a small risk of periprocedural complications [23]. Considering the availability of CT and MRI, conventional angiography is not commonly used for the diagnosis of CVT. In rare cases of isolated thrombosis of the cortical vein or non diagnostic from the CT or MRI brain, angiogram may be useful in diagnosis CVT [26].

**Treatment of Intracerebral Hemorrhage from CVT (Table 2)**

**Anticoagulation Therapy**

Studies on anticoagulation in patients with ICH are scarce. In uncontrolled studies, anticoagulation was associated with a small risk of new intracerebral hemorrhage 3.6 % [8]–5.4 % [27]. There were two small controlled trials that reported the efficacy and safety of anticoagulation therapy. Some patients received anticoagulation despite having an ICH related to CVT. Einhaupl et al. [27] studied 20 patients with CVT, comparing dose-adjusted intravenous heparin...
with placebo. In the heparin group, 8 patients recovered completely and none died. In the placebo group, 1 patient recovered fully and 3 patients died. There were 3 patients whom previously had ICH and received heparin and had recovered completely with no recurring hemorrhage. Bruijn et al. [28] had studied 60 patients with CVT, comparing between body weight adjusted subcutaneous LMWH and placebo, it was found that 3 patients (10%) in the LMWH group and 6 patients (21%) in the placebo group had poor outcome after 3 months. There was no new ICH or secondary worsening of the 15 patients with pre-treatment hemorrhage that received LMWH. There was one major extracerebral hemorrhage in the heparin group. A meta-analysis including these two trials showed that anticoagulant therapy was associated with a non-significant lower risk of death (RR 0.33; 95% CI 0.08–1.21) and death or dependency (RR 0.46; 95% CI 0.16–1.31). The absolute risk reduction of death or dependency was 13% (95% CI 30% -3%) [29]. Despite not reaching significance, there was, however, a trend towards the benefit of anticoagulation therapy. The AHA (American Heart Association) guidelines support anticoagulation therapy in treatment of CVT despite of the presence of pretreatment ICH [9••]. In addition, EFNS (European Federation of Neurological Societies) guideline also recommended that patients with CVT, without contraindications for anticoagulation therapy, should be treated either with body weight- adjusted LMWH or dose adjusted intravenous heparin with at least a double activated partial thromboplastin time, ICH related to CVT isn’t a contraindication for anticoagulation therapy [24••].

Table 2 Treatment of Intracerebral Hemorrhage from CVT

<table>
<thead>
<tr>
<th>AHA guideline [9••]</th>
<th>EFNS guideline [24••]</th>
<th>Chest guideline [36••]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anticoagulation Therapy (despite ICH)</td>
<td>● (Class IIa)</td>
<td>● (Class IIb)</td>
</tr>
<tr>
<td>Intrasinus thrombolysis</td>
<td>* (Class IIb)</td>
<td>NR</td>
</tr>
<tr>
<td>Mechanical thrombectomy</td>
<td>* (Class IIb)</td>
<td>NR</td>
</tr>
<tr>
<td>Mechanical thrombectomy/thrombolysis</td>
<td>* (Class IIb)</td>
<td>NR</td>
</tr>
<tr>
<td>Routine anticonvulsants prophylaxis for all patients w/CVT</td>
<td>● (Class III)</td>
<td>● (Class III)</td>
</tr>
<tr>
<td>Anticonvulsants in patients with CVT and supratentorial lesions without seizure</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Anticonvulsants in patients with CVT with both supratentorial lesions and Seizures</td>
<td>● (Class I)</td>
<td>NR</td>
</tr>
<tr>
<td>Anticonvulsants in patients with CVT without parenchymal lesions and Seizures</td>
<td>● (Class IIa)</td>
<td>NR</td>
</tr>
</tbody>
</table>

AHA American Heart Association; EFNS European Federation of Neurological Societies; ICH intracerebral hemorrhage; NR not reported in intracerebral hemorrhage from CVT

*Mechanical thrombectomy/thrombolysis may be considered in patients with neurological deterioration despite intensive medical treatment.

Fig. 3 A 38-year-old woman presented with alteration of consciousness; a Noncontrast CT brain axial image showed hemorrhagic transformation at left frontal lobe (b) Noncontrast CT brain axial image showed left frontal craniotomy and massive multifocal hemorrhagic at left frontal lobe, severe mass-effect on the midline structures and basal cisterns. Her CT venogram showed thrombosis of left frontal cortical veins.
Thrombolyis

Intrasinus Thrombolysis is used in CVT patients who have clinically deteriorated despite anticoagulation therapy. However, there is no evidence from randomized controlled trials about the efficacy and safety of thrombolytic therapy. Frey IL et al. [30] studied 12 CVT patients whom received bolus injection of rtPA directly to the thrombus and followed by continue infusion. There were 2 patients with pre-treatment ICH that had increased intracerebral bleeding which required surgery. Therefore, even though there is faster reconstitution venous flow, intrasinus thrombolysis may carry higher risk of bleeding complications compared to anticoagulant therapy especially in pre-treatment ICH group [24••].

Mechanical Thrombectomy/Thrombolysis

Mechanical thrombectomy/Thrombolysis is usually reserved for patients with neurological deterioration despite intensive medical treatment [9••]. Currently, there are no large randomized controlled trials to determine the efficacy and safety of mechanical thrombectomy/thrombolysis in patients with cerebral hemorrhage related to CVT. The benefit from thrombectomy in cerebral hemorrhage due to CVT was only reported in case reports and small case series [31–33]. In a prospective study of 20 patients who had severe CVT and received the combination of thrombectomy and thrombolysis, good outcome (mRS0-2) was reported in 60 %. However, increase in intracerebral hemorrhage was found in 25 % [34]. In AHA guideline, direct intrasinus thrombolytic and mechanical therapies may be considered in patients who developed clinical deterioration despite use of anticoagulation or if the patient develops mass effect from a venous infarct or ICH [9••].

Seizures

Seizures are a common complication in CVT, in ISCVT study, seizure was found in 39 % of 624 CVT patients [5]. Girot et al. [11] reported that seizure is frequently found in CVT with ICH comparing without ICH (55 % VS 29 %, P=0.000). In Ferro et al. [35] study reported focal sensory deficits and the presence of focal edema or ischemic/hemorrhagic infarcts on admission CT/MRI brain is a significant predictors of early symptomatic seizures. However, anticonvulsants for prophylaxis seizure in CVT is still controversial. In EFNS guideline has recommended prophylactic antiepileptic therapy in patients with focal neurological deficits and supratentorial lesions on admission CT/MRI [24••] which is in contrast of AHA guideline [9••]. The AHA guidelines recommend anticonvulsant in patients with acute CVT with supratentorial lesions who present with seizure [9••].

Outcome

In the past 20 years the mortality rate associated with cerebral venous sinus thrombosis has dramatically decreased. This phenomenon is likely related to early recognition of the clinical presentation, early diagnosis, improvement in non-invasive imaging, and effectiveness of treatment options. The mortality rate was reported in 4.39 % to 8.3 % [5, 7, 8]. However, cerebral hemorrhage related to CVT is one of the factors associated with unfavourable outcome (Fig. 3). Patients with ICH related CVT may have a twofold likelihood of death of dependency compared with CVT patient without ICH. In the ISCVT study, age >37 years (HR=2.0, 95 % CI 1.23–3.27), male (HR 1.59, 95 % CI 1.01–2.52), mental status disorder (HR 1.95, 95 % CI 1.23–3.09), GCS <9 (HR 2.65, 95 % CI 1.41–4.55), hemorrhage on admission (HR 1.88, 95 % CI 1.17–3.03), thrombosis of the deep cerebral venous system (HR 2.92, 95 % CI 1.7–5.0), central nervous system infection (HR 3.34, 95 % CI 1.98–17.24), and cancer (HR 2.90, 95 % CI 1.6–5.08) were associated with death and dependency [5]. In the subgroup analysis from the ISCVT study, it was found that patients who had early ICH in CVT had a significantly higher in death rate 6 % comparing in patients without ICH 2 %; (p=0.002) and poor outcome (mRS 3–6 at 6 months: 21 % ICH vs 9 % without ICH; (p<0.001) [11]. More recently, in a larger study including 3,488 patients with CVT, Haghighi et al. [7] reported ICH as one of the predictors of mortality (OR 1.78; 95 % CI 1.04–3.05).

Conclusions

Cerebral venous thrombosis is uncommon cause of stroke. However, it may cause serious neurological complications (e.g. ICH, seizures, etc.) especially in patients whom diagnosis is delayed. CVT presenting with intracerebral hemorrhage may be a challenging scenario. A high clinical suspicion is needed for young patients presenting with ICH to avoid potential pitfall in the diagnosis of CVT. Early recognition of risk factors, clinical presentations, and brain imaging patterns may help the diagnosis CVT. According to the Guidelines, anticoagulation therapy is the first line of treatment in intracerebral hemorrhage from CVT.

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References

Papers of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance
