Cerebral venous thrombosis

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Summary

Cerebral venous thrombosis (CVT) has an incidence of 1.32/100,000/years in high-income countries, and higher in middle- and low-income countries. CVT is more frequent in infants and children young adults and females, especially during pregnancy/puerperium. CVT are now being diagnosed with increasing frequency because of the increased awareness and higher use of magnetic resonance imaging (MR) for investigating patients with acute and subacute headaches and new onset seizures. CVT rarely present as a stroke syndrome. Their most frequent presentations are isolated headache, intracranial hypertension syndrome, seizures, a lobar syndrome and encephalopathy. The confirmation of the diagnosis of CVT relies on the demonstration of thrombi in the cerebral veins and/or sinuses by MR/MR venography or veno CT. The more frequent risk factors/associated conditions for CVT are genetic prothrombotic conditions, antiphospholipid syndrome and other acquired prothrombotic diseases, including cancer, oral contraceptives, puerperium and pregnancy, infections and trauma. The prognosis of CVT is in general favorable, as acute death rate is below 5% and only 15% of the patients remain dependent or die. Treatment in the acute phase includes management of the associated condition, anticoagulation with either low molecular weight or unfractionated heparin, treatment of intracranial hypertension, prevention of recurrent seizures and headache relief. In patients in severe condition on admission or who deteriorate despite anticoagulation, local thrombolysis or thrombectomy is an option. Decompressive surgery is lifesaving in patients with large venous infarcts or hemorrhage with impending herniation. After the acute phase, patients should anticoagulated for a variable period of time, depending on their inherent thrombotic risk. CVT patients may experience recurrent seizures. Prophylaxis with anti-epileptic drugs is recommended after the first seizure, in those with hemispheric lesions. There are several ongoing multicenter registries and trials, which will improve evidence-based and patient-centered management of CVT in the near future.

Definition

While for neurologists, thrombosis of the dural venous sinus or of the cerebral veins are regarded as a special type of stroke, for vascular surgeons and hematologists, they are considered as a...
venous thrombosis in a special anatomical location [1]. Cerebral
vein and dural sinus thrombosis (CVT) are in fact an example of
venous thrombosis in an uncommon location, in this regard
similar to splanchic venous thrombosis. CVT are also a venous
thrombosis with a special pathophysiology, due to the lack of a
role for hydrostatic gravitational pressure in CVT, in contrast to
what happens in the much more common deep venous thrombosis
of the lower limbs.

Contrasting CVT with arterial stroke, a few key aspects are
apparent:
- CVT are less common but they can be easily missed and their
diagnosis is often delayed;
- CVT affects much younger patients with a female predominance
  (figure 1);
- CVT has in general a non-apoplectic onset, rarely present as a
  stroke syndrome, but has a wider spectrum of clinical presenta-
tion syndromes;
- CVT has multiple risk factors and associated conditions, which
  are different from those of arterial stroke;
- CVT has a different treatment, similar to systemic deep venous
  thrombosis, consisting mainly of parenteral heparin followed
  by oral anticoagulation;
- CVT has a much more favorable outcome

**Epidemiology**

CVT is less frequent than ischemic stroke and also than intracere-
bral or subarachnoid hemorrhage. The older studies of CVT
prevalence were autopsies studies. They reported a high preva-
ience of 1-9% CVT as a post-mortem finding often asymptomatic
during life [2]. A mortality study performed in the UK from
1952 to 1961 reported an average of 22 cases of fatal CVT
annually and a death rate due to CVT of 0.39 per million [3].
These high figures reflect selection bias for severe fatal cases
and high rates of CVT associated with infections.

More recent studies were mainly hospital bases series. In a
cooperative study of Neurology centers in Portugal, a CVT inci-
dence of 0.22/100,000/year was reported [4]. A higher inci-
dence was reported in Isfahan, Iran (1.23/100,000/year) [5].
The epidemiological study of CVT with the more valid method-
ology was performed in the Netherlands and found an overall
incidence of 1.32/100,000/year and of 2.78 for women
between the ages of 31 and 50 [6]. The higher incidence found
in this study probably reflects a higher detection rate and a more
complete case ascertainment. This incidence is similar to that of
bacterial meningitis in adults. Higher incidences of CVT are found
in infants and children, in young adults and in females. In
contrast to other stroke subtypes, the incidence of CVT decreases
with age. A systematic review including of 8829 CVT patients
from 74 series with more than 40 subjects found an average age
of 32.9 years and 64.7% of women [7]. CVT is also more frequent
in low-middle income countries, in particular in those with high
pregnancy rates. In fact, CVT represented 3% of 2000 strokes in a
Stroke Registries in Mexico [8]. Rates of CVT during pregnancy
also show high: 11.6/100,000 deliveries in the USA [9] and
more than half of all strokes among pregnant women (136/240
[57%]) in Mexico [10]. A higher incidence (0.64/100,000) was
also reported in infants and children < 18 years in Canada [11].
Due to increased awareness and easier access to magnetic
resonance imaging (MR) for investigating patients with acute
and subacute headaches and new onset seizures, CVT are now
being diagnosed with increasing frequency. A systematic review
of CVT series with more than 40 patients showed a clear trend in
declining mortality in patients with CVT over time [12]. The
frequency of focal neurological deficits and coma also decreased
significantly over time. Declining in mortality can be due to
better management, a decrease in septic CVT, but most probably
is mainly due to the identification of less severe cases by MRI.
There are however several reasons to suspect that the incidence
of CVT is still underestimates. CVT have a more varied clinical
presentation than other stroke types and hence they are more
difficult to recognize. In particular, in the two extremes of their
clinical spectrum of severity, CVT may easily be missed. CVT
patients complaining only of headache may usually have a
benign auto-limited course [13] and CVT will not be diagnosed
unless CT plus CT venography or MR plus MR venography are
performed. On the other hand, in severely ill or terminal patients
(e.g. cancer), headache may be absent [14] and new or wors-
ening neurological signs may be attributed to other causes
(metastatic, metabolic or infectious) and neuroimaging to rule
out CVT may deemed not necessary.

**Anatomy of the brain venous system**

The cerebral venous drainage pattern does not correspond to
cerebral arterial territories and is often asymmetric (figure 2).
The variability of the superficial Sylvian vein and anastomotic
vessels prevents a precise delimitation of the territory of each dural sinus.

Veins of the cerebral hemisphere
Brain parenchyma is drained mainly by cortical and medullary veins which empty either into veins on the cortical surface or into the deep venous system (figure 3).

Superficial veins
The superficial group runs centrifugally, draining the cortex and subcortical white matter [15] into the superior and inferior sagittal, straight, transverse, tentorial, cavernous, sphenoparietal, sphenobasal and sphenopetrosal sinuses.

The largest veins on the lateral surface of the brain are the middle cerebral (or superficial Sylvian vein), the superior anastomotic vein (of Trolard) and the inferior anastomotic vein or temporo-occipital vein (of Labbé). These anastomotic veins show reciprocal prominence, so that when one is large on a given side, the others are usually small [16].

Deep supratentorial veins
The deep venous system may also be defined as the entire territory served by the great vein (of Galen) and the basal veins (of Rosenthal). The deep medullary veins are very small intracortical veins with a radial and centripetal course toward the lateral ventricles, converging into several subependymal veins. The deep veins collect blood from the central structures of the hemispheres, surrounding the lateral and third ventricles and the basal cisterns, namely the basal ganglia, corpus callosum, pineal region, part of the limbic system (including the cingulate and parahippocampal gyri), part of the visual cortex, the
diencéphalon and rostral brain stem and part of the cerebellum, delivering it to the internal jugular veins [17] (figure 4). The deep venous system is more constant compared to the superficial cortical venous system.

**Dural sinuses**

The dural sinuses lie between endothelial-lined layers of dura, a meningeal layer with little compliance, lacking valves and typical vessel wall layers. These features make the intracerebral venous compartment less dependent on variations in venous pressure than other organs of the body [18]. The named sinuses are the superior and inferior sagittal, straight, transverse, sigmoid, occipital, cavernous, intercavernous, superior and inferior petrosal, sphenoparietal, basilar and marginal. Two groups of dural venous sinuses, a superior and an inferior, can be distinguished (figure 2). The dural sinus can also have several individual anatomical variations, the most common being the asymmetry of the lateral sinus, which is often of smaller caliber, hypoplastic or even atretic on the left side [19].

**Superior group**

The superior group includes the superior and inferior sagittal sinuses and the straight, occipital, transverse and sigmoid sinuses. This group drains the majority of the brain and skull. Its confluence is at the torcular Herophili with subsequent drainage via the transverse and sigmoid sinuses into the jugular veins.

**Inferior group**

The inferior group includes the sphenoparietal and cavernous sinuses, the superior and inferior petrosal sinuses and the basilar plexus. The blood is collected at the cavernous sinuses and

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**Figure 3**

MR venography (phase-contrast) in a patient with extensive sinus thrombosis. Increased collateral circulation through veins of the superficial and deep system can be seen. The patient did not develop any brain lesion.

**Figure 4**

Thrombosis of the cerebral deep venous system (straight sinus and internal cerebral veins) associated with bilateral thalamic venous infarction (MRI FLAIR). Enlarged venous spaces, called lacunae, are contained in the dura mater adjoining the superior sagittal sinus (SSS). The arachnoid (pacchionian) granulations project into the floor and walls of the lacunae, which increase with age [20]. Venous lacunae receive blood from meningeal, diploic and emissary veins and cerebrospinal fluid from the arachnoid granulations and drain into the dural sinus. Although the SSS is classically described to converge with the straight sinus at a plexiform confluent venous complex, called the torcular Herophili (sinus confluens), where their combined flow drains into the transverse sinuses, there are numerous variations in the pattern of confluence of the superior sinus group [21]. In most cases, the drainage of the SSS occurs predominantly or entirely into one of the transverse sinuses, with the right side being estimated to be the dominant in three quarters of the subjects. Accordingly, the straight sinus generally drains predominantly into the opposite lateral sinus (left side three times more often than right). Particularly in infants, the superior sagittal sinus may communicate with the inferior sagittal sinus through veins that lie within the falk.
drains either into the pterygoid plexus or via the inferior petrosal sinuses and the basilar and internal vertebral plexuses into the sigmoid sinus and jugular vein. The paired cavernous sinuses lie lateral to each side of the sella turcica. Besides being connected across the midline by the intercavernous sinuses, the cavernous sinuses have several anastomosis [22] and important anatomical relationships, as the cranial nerves III, IV, V1 and V2 travel in the lateral wall of the sinus and the internal carotid artery, sympathetic plexus and cranial nerve VI lie suspended by fibrous trabeculae within the sinus lumen. Evidence from several works supports that the principal outflow through the internal jugular veins can be substituted completely by the large vertebral plexuses through communications at the cranial base [17]. A dominant role of the vertebral venous system in cerebral venous drainage in the upright position was also shown more recently, in association with a physiological collapse of the internal jugular vein that stimulates the collateral outflow pathway [23-25].

**Diploic and emissary veins**

The diploic veins are endothelial-lined venous channels lying within the diploic space. The emissary veins transverse cranial apertures making connections between intracranial venous sinuses and extracranial veins and may be associated with spread of infections from extracranial foci (e.g. mastoid or paranasal sinus infections) to venous sinuses. These connections are also of clinical significance because they may provide important collateral pathways in dural venous thrombosis.

**Veins of the posterior fossa**

The great cerebral veins, torcular Herophili, transverse and superior petrosal sinuses receive the venous drainage from the cerebellum. The venous drainage of the brain stem has a pattern comparable to that of the arterial supply [26].

**Pathophysiology**

The hemodynamic and brain tissue changes underlying the pathophysiology of cerebral veins and sinus thrombosis (CVT) are complex and remain incompletely understood [27]. The limitations of animal models of CVT [28,29] and the anatomical variations in the brain venous system certainly contribute to this knowledge deficit. Development of venous thrombosis is associated with a systemic or local aetiology that, ultimately, causes an imbalance of prothrombotic and thrombolytic processes, leading to thrombus initiation and propagation in cerebral dural sinuses or veins. This occlusion forces venous blood back into small vessels and capillaries. If venous drainage is sufficiently obstructed, local ischemia occurs followed by cerebral edema and hemorrhagic infarction [30]. However, as previously described (vd “Anatomy of the venous system”), the venous territories of the brain are less well defined than the arterial territories due to anatomical variations and the presence of extensive anastomoses that often allow the development of collateral circulation when there is an obstruction to the venous flow. Therefore, if anastomotic channels are present, the recruitment of collateral pathways may, to a certain extent, compensate for changes in pressure (figure 3). Progressive hyperperfusion was observed in experimental models of CVT, supporting the hypothesis that perfusion of the affected brain tissue is still possible in the initial phases of CVT through collateral drainage pathways [31,32]. Accordingly, venous occlusion result in the development of parenchymal brain changes in approximately 60% of the cases of CVT [33] (figure 4). Data from experimental models of CVT and from imaging analysis of affected patients suggest that, in these cases, the increase in venous and capillary pressure leads to blood-brain barrier disruption, causing vasogenic edema, with leakage of blood plasma into the interstitial space. Decreased cerebrospinal fluid (CSF) absorption due to the dysfunction of arachnoid granulations associated with occlusion of dural sinuses may also be another mechanism contributing to elevated intracranial pressure [34]. If intravenous pressure continues to increase, capillary hypertension develops and mild parenchymal changes, severe cerebral edema, and venous hemorrhage may occur, due to venous or capillary rupture [35]. The increased intravenous pressure may finally lead to a lowering of cerebral perfusion pressure, resulting in decreased cerebral blood flow and failure of energy metabolism. Failure of the Na’K+ ATPase pump will ultimately allow for intracellular entry of water and consequent cytotoxic edema [36]. Although some authors have proposed that venous occlusion involving the confluent portion of collecting venules and veins was critical for the development of severe brain parenchymal lesions, particularly hemorrhage [36], this was not confirmed in experimental models in which venous infarction could be induced only with occlusion of a single sinus [32]. The important role of intrasinus venous hypertension in the pathophysiology of cerebral venous infarction is also further supported by the observation that venous pressure is directly associated with the degree of parenchymal changes [27,37]. Analysis of a large clinical cohort has also shown that although the association between the severity of the associated clinical syndrome and the extent of the thrombosis is much more variable in CVT than in arterial occlusion, a significant association between the thrombus load and the development of brain lesion is still found [38]. Besides, different patterns of thrombosis are associated with distinct risks of brain parenchymal lesion related to CVT [38]. On the other hand, although increase in intracranial pressure is a classical clinical feature in patients with CVT, its contribution for the pathophysiology of most brain lesions is not well established [36].

Most patients with CVT have a gradual worsening or onset of new symptoms over days or weeks [33]. This evolution should be related with a subacute progression of the thrombosis...
and/or failure of the venous collateralization or other possible compensatory mechanisms that kept the perfusion pressure above minimal thresholds in the initial stages. The presence of clots of various ages in autopsy studies of patients with CVT supports the hypothesis that ongoing progression of thrombosis is also part of the pathophysiology of CVT, at least in some of the patients with subacute worsening. Systemic factors and venous stasis of the affected vascular bed might contribute to thrombus propagation [27]. The experimental and clinical observation of recovery in a significant proportion of patients indicates that in CVT affected areas of the brain can be functionally and metabolically disturbed without being irreversibly damaged [39]. Experimental studies suggested that cytotoxic edema is a primary phenomenon, with vasogenic edema occurring as a secondary manifestation [40] and data from diffusion-weighted imaging (DWI) MRI studies in patients with CVT has shown the coexistence of both cytotoxic and vasogenic edema in acute cases [41]. Anecdotal reports of full recovery in brain lesions with reduced ADC values in patients with CVT confirm that the interpretation and prognostic value of ADCs suggesting cytotoxic edema do not parallel those of arterial stroke [42]. This different pathophysiological pathway of venous infarction suggests that possible treatment options might show efficacy during a larger time window than what is usually expected for brain arterial ischemic disease [27]. Concerning the role of recanalization and increased collateralization in the outcome and recovery from CVT, a significant univariate association between clinical outcome and recanalization in patients with CVT was shown in a recent systematic review [43].

No impact of baseline intracranial venous collaterals on the type of brain damage, clinical manifestations or prognosis of patients with CVT was shown in a retrospective cohort study [44]. Further investigation is warranted to clarify the role of recanalization and collateralization in the recovery of patients with CVT, as these findings should have important implications in the therapeutic strategies.

**Etiology**

Cerebral venous thrombosis is a multicausal disease, and may be triggered by the interaction of several risk factors. Some of them are permanent and non-modifiable, such as inherited thrombophilia, whereas others are circumstantial or precipitant, such as pregnancy or infection. In the ISCVT, at least one risk factor was identified in more than 85% of adult patients with CVT, and multiple risk factors were found in about half [33]. In the Canadian Pediatric Ischemic Stroke Study Group, a risk factor was identified in 98% of the children [11].

Many conditions or risk factors are associated with CVT (table I). The most common are genetic or acquired prothrombotic disorders, gender-specific risk factors, malignancy, infections and inflammatory diseases.

Prothrombotic disorders are leading risk factors for CVT. The most frequent are G20210A prothrombin polymorphism (identified in 6% to 20% of patients with CVT), [45–48] factor V Leiden (10 to 24%), [46–52] and antiphospholipid syndrome (6 to 8%) [33,49]. Less often, protein C, protein S, or antithrombin III deficiencies may be revealed (0 to 9%) [46–51]. A systematic review of case-control studies confirmed the increased risk of CVT in patients with G20210A prothrombin polymorphism

<table>
<thead>
<tr>
<th>Table I</th>
<th>Risk factors and associated conditions for cerebral venous thrombosis</th>
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<tr>
<td><strong>Permanent risk factors</strong></td>
<td><strong>Transient risk factors</strong></td>
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<tr>
<td>Genetic thrombophilia: prothrombin G20210A mutation; factor V Leiden mutation; protein C deficiency; protein S deficiency; antithrombin deficiency</td>
<td>Gender-related risk factors: oral contraceptives; pregnancy and puerperium; replacement hormonal therapy</td>
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<tr>
<td>Hematological diseases: paroxysmal nocturnal hemoglobinuria; sickle cell disease or trait; polycythemia vera; essential thrombocythemia</td>
<td>Infections: intracranial infection; ear, sinus, mouth, face and neck; systemic infectious disease (e.g., sepsis, endocarditis, tuberculosis, HIV)</td>
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<tr>
<td>Malignancy: central nervous system; solid tumor outside the CNS; leukemia and lymphoma</td>
<td>Systemic conditions: severe dehydration; severe anemia; diabetic ketoacidosis</td>
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<td>Vasculitis and related disorders: antiphospholipid syndrome; Behçet’s disease; systemic lupus erythematosus; Sjögren’s syndrome; Wegener’s granulomatosis; temporal arteritis; thromboangiitis obliterans</td>
<td>Drugs: hormone therapy (glucocorticoids, androgens); chemotherapy (cyclophosphamide, cyclosporine); hormonal therapy (tamoxifen); angiogenesis inhibitors (thalidomide); hemostatic treatments</td>
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<tr>
<td>Inflammatory and other conditions: inflammatory bowel disease; sarcoidosis; nephrotic syndrome; thyroid disease</td>
<td>Mechanical causes: head trauma; lumbar puncture; myelography; jugular catheter occlusion; neurosurgical procedures; irradiation</td>
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<tr>
<td>Intracranial causes: meningioma; dural fistula</td>
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</table>
Cerebral venous thrombosis

(pooled odds ratio [OR] 5.48, 95% confidence interval [CI], 3.88–7.74), and in patients with Factor V Leiden mutation (pooled OR 2.40; 95% CI, 1.75–3.30) [53]. Another systematic review showed that this association may depend on the country of origin: the prevalence of prothrombin G20210A was significantly elevated in Italian studies (OR 9.69), in Brazilian studies (OR 7.02), and in German studies (OR 3.77), but not in Iranian studies (OR 0.98) [54]. Likewise, in the pediatric setting, a systematic review of case-control studies showed that both carriers of the FVL mutation and of the prothrombin gene mutation were significantly more likely to develop CVT (pooled OR 3.1, 95% CI 1.8–5.5, and 3.1, 95% CI 1.4–6.8, respectively) [55].

Hyperhomocysteinemia was shown to be associated with increased risk of CVT (pooled OR, 4.07, 95% CI 2.54–6.52) [56]. The contribution of methylene tetrahydrofolate reductase (MTHFR) C677T gene homozigoty as a risk factor for CVT is controversial, but a systematic review with an iterative analysis controlling for interstudy heterogeneity, suggested an increased risk of CVT (pooled OR 2.30, 95% CI 1.20–4.42) [53].

The following gender-specific risk factors explain the high frequency of CVT in women: oral contraceptives, pregnancy or puerperium, and hormonal replacement therapy. Oral contraceptives are the most frequent risk factor for CVT in women. In the ISCVT, 54% of women under 50 reported using oral contraceptives. A meta-analysis showed that the risk of CVT in women taking oral contraceptives was almost six times higher than that of non-users (OR 5.59; 95% CI, 3.95–7.91) [56]. Overweight and obesity were shown to be associated with an increased risk of CVT in women who used oral contraceptives, in a dose-dependent manner [57]. Among oral contraceptive users, the thrombotic risk is even higher among carriers of hereditary thrombophilias (e.g. factor V Leiden, the prothrombin gene mutation, and deficiencies of protein S, protein C, and antithrombin) [48,50]. Another frequent setting related to CVT in women is pregnancy and (more frequently) the puerperium [33,58,59], more common in less developed world regions. CVT has also been diagnosed in association with the ovarian hyperstimulation syndrome resulting from in vitro fertilization [60].

Infected causes of CVT have declined, being responsible for 6–12% in large series of adults [2,33]. It is more common in middle- to lower-income countries, where its prevalence is between 18% and 34% [61–63]. The most common infections associated with CVT are otitis, mastoiditis and sinusitis. Although uncommon, cavernous sinus thrombosis is caused predominantly by skin infections of the face.

Cancer accounts for about 7% of CVT [33]. Sinus or venous thrombosis can result from local compression or invasion by the tumor, can be caused by a hypercoagulable state, or, less commonly, can be associated with local or systemic infections, can be therapy related, or be paraneoplastic [64]. Several chemotherapeutic agents used in the treatment of patients with malignancy have been associated with cerebral venous thrombosis. The best-known associations with thrombosis are L-asparaginase, which is typically used in the induction therapy of acute lymphocytic leukemia, and combination hormonal therapy and chemotherapy for breast cancer. Cerebral vein thrombosis can be the first symptom of a solid cancer, particularly if the tumour is located in the brain, and of myeloproliferative neoplasms [65].

Most of the precipitants of CVT are systemic diseases or conditions predisposing to venous thromboembolism, but some are specific for CVT. Among these are local causes, such as brain tumors, arteriovenous malformations, regional infections, major or minor head trauma, spontaneous intracranial hypotension, and some invasive procedures (e.g., neurosurgery, jugular catheterization, irradiation, and lumbar puncture with or without drug infusion).

The risk factors of CVT vary throughout life. In neonates, acute systemic illness, such as perinatal complications and dehydration were frequent, occurring in 84% of patients [11]. Head and neck disorders, mostly infections, and chronic systemic diseases (e.g., connective tissue diseases, hematologic disorders, and cancers) were common in older children. A prothrombotic state was found in 41% of the patients, most often in non-neonates. In elderly patients, the proportion of cases with malignancies and hematological disorders, such as polycythemia is higher, whereby search for an occult neoplasm may be considered. No underlying etiology or risk factor for CVT is found in approximately 15% of adult patients. The cause may be revealed weeks or months after the acute phase. Therefore, it is recommended to monitor the patient and to continue searching for a cause (the antiphospholipid syndrome, polycythemia, thrombocytopenia, or malignancy).

Clinical features

As stated above, the clinical presentation of CVT is highly variable. The mode of onset of CVT can be acute, but is rarely “stroke-like”. More often onset is subacute and less frequently chronic [33].

Symptoms and signs of CVT can be grouped in presenting syndromes, the most frequent ones being isolated intracranial hypertension syndrome, focal syndrome and encephalopathy [66]. Less frequent presentation syndromes are cavernous sinus syndrome or syndromes of multiple palsies of the lower cranial nerves (VII, Collet-Sicard syndrome). The syndrome of isolated intracranial hypertension features headache with or without vomiting, papilledema and visual obscurations, decreased visual acuity or enlargement of the blind spot or concentric restriction of the peripheral visual fields, and less often tinnitus and VI nerve palsy. Papilledema and visual loss are more frequent in cases with chronic onset who present late. Headache is the most frequent symptom of CVT and usually the initial one. A reasonable proportion of CVT patients, in particular those who come early to medical attention complain only of headache (isolated
headache) [67]. As headache in general, headache associated with CVT is more frequent in women and in younger patients. The most frequent type of headache is the intracranial hypertension type, a severe, generalized headache of progressive onset, persistent worsening with straining, Valsalva’s maneuvers and when the patient is lying down [68]. In a few cases of CVT, headache as the features of migraine aura [69] or of thunderclap headache [70]. A few cases presenting as non-aneurysmal subarachnoid hemorrhage, either generalized or localized to a single or few cortical sulci of the hemispheric convexity have been reported [71]. While CVT patients with generalized subarachnoid hemorrhage present in general with sudden, explosive headache and display stiff neck, those with convexity subarachnoid hemorrhage have a more complex symptomatology. In a series of 10 cases, all due to superior sagittal sinus thrombosis, all patients had headache, 9 experienced seizures, 4 had papilledema and only 4 presented meningeal signs [72]. There are few studies detailing the characteristics of headache due to CVT. In a retrospective study of 200 cases, Wasay et al. [73] described headaches with varied quality (band-like, throbbing and thunderclap) and location (localized, unilateral of diffuse). There is in general no association between the site of venous thrombosis or of the associated brain parenchymal lesions and the location of the headache. Using a headache questionnaire in 25 CVT patients, Sparaco et al. [74] describe headache as typically severe, throbbing, with sudden onset and non-remitting.

Other patients present as a focal syndrome, i.e., a focal deficit, such as paresis or aphasia, seizures or both. Hemianopia and other sectorial visual field defects are uncommon as well as cerebellar signs. Seizures can be focal or reported as generalized from onset and may evolve to status epilepticus. Seizures are more frequent in patients with supratentorial lesions, in particular if hemorrhagic, and in those with motor and sensory deficits and superior sagittal sinus or cortical vein thrombosis [4,33,75,76]. CVT should always be considered in the differential etiological diagnosis of a new onset seizure in the young and middle aged adult.

The more severe presentation syndrome of CVT is encephalopathy. These patients have decreased consciousness, mental status disturbances, including delirium, apathy or dysexecutive symptoms, bilateral or multifocal signs, and/or seizures. Some of these patients are comatose. Comatose patients usually have multiple sinus occlusion, in particular combining the superior sagittal sinus and the deep cerebral vein system and show bilateral parenchymal lesions and diffuse brain edema or a large herniating lesion. Seizures and status epilepticus as the cause of decreased consciousness or coma should be ruled out. Two series of severe CVT needing intensive care recently published confirmed this description [77,78].

The clinical presentation of CVT varies according to the age of the patient, the time to diagnosis, the presence of parenchymal lesions and the venous topography of the thrombosis. Encephalopathy is more frequent is elderly patients, while headache is less frequent [79]. Isolated intracranial hypertension and papilledema are more frequent in patients with a late, chronic presentation [80,81]. There is a gradient of increasing clinical severity from patients without brain lesions to patients with non-hemorrhagic lesions and hemorrhagic lesions [82,83]. Motor deficits, seizures, mental status disorders and decreased consciousness are more frequent in patients with brain lesions, while isolated intracranial hypertension syndrome is rarer. In general, CVT involves more than a single vein or sinus. Nevertheless, some general clinical patterns can be established accordingly to the topography of the occluded sinus and veins (figure 5). In cavernous sinus thrombosis, there is usually headache, orbital pain, chemosis, proptosis, ptosis, diplopia and oculomotor palsies. Typically, cortical vein thrombosis produces motor and or sensory deficits and seizures [84]. A recent systematic review of 116 patients with isolated cortical vein thrombosis [7] confirmed that the most common symptoms/signs of isolated cortical vein thrombosis were headache, seizures and focal neurological deficits. No patients had papilledema. In the occlusion of the sagittal sinus, motor deficits can be unilateral or bilateral, and focal or generalized seizures are frequent. Patients with isolated thrombosis of the lateral sinus often present as isolated intracranial hypertension, but aphasia is frequent in left transverse sinus occlusion. If the deep cerebral venous system is thrombosed, the clinical picture is often severe with coma, mental deficits and paresis. A few cases of partial occlusion of the deep venous system were also reported [85]. Such patients had a milder clinical picture with headache, hemiparesis, aphasia, visual field defect or mental status disturbance, but no decreased consciousness. Occlusion of the cerebellar veins is uncommon and has usually a subacute presentation. The majority of these patients have an intracranial hypertension syndrome, but less than half have a cerebellar syndrome [8,86].

**Brain imaging and confirmation of the diagnosis**

The confirmation of the diagnosis of CVT depends on the demonstration of thrombi in the cerebral veins or sinuses. Three imaging techniques can be used: magnetic resonance imaging (MRI) with MR venography, computerized tomography (CT) with CT venography, and angiography [87].

**Magnetic resonance imaging – MR venography**

Magnetic resonance imaging (MRI) in combination with magnetic resonance venography (MR venography) has become the non-invasive imaging technique of choice. The diagnosis requires visualization of the thrombus within the vessel in combination with absent flow on MR venography. A panel of several MRI techniques in addition to MR venography, rather an isolated technique, can significantly enhance the accuracy of the
diagnosis. Administration of contrast material and application of specific MR sequences and venographic techniques are often required for a confident diagnosis.

**Magnetic resonance imaging**

MRI allows visualization of the thrombus within the sinus or veins (*figures 6 and 7*). The MRI signal can vary on different sequences according to the age of the thrombus: in the first 5 days, the signal is isointense on T1-weighted images and hypointense on T2-weighted images; after this time, there is an increased signal on both T1- and T2-weighted images (*figure 7*). After the first month, there is a variable pattern of signal, which may more frequently become isointense or hyperintense on T2-weighted images and hypointense or isointense on T1 [88,89]. Gradient-echo T2* and susceptibility-weighted imaging (SWI) sequences improve the diagnosis of CVT, enabling the identification of intraluminal thrombus as a hypointense area (*figure 8*). [90–93]. These sequences are particularly useful in the acute stage of dural sinus thrombosis and in the diagnosis of cortical vein thrombosis [94]. The use of SWI may be outstanding in the diagnosis of isolated cortical vein thrombosis because this sequence may demonstrate a thrombus in a cortical vein [94]. A chronically thrombosed sinus may still demonstrate low signal on these sequences.

Recently, a promising magnetic resonance black-blood thrombus imaging (MRBTI) technique was proposed to achieve accurate detection of thrombus in the cerebral venous system. Blood signal is suppressed using MRBTI, and thrombi are depicted as hyperintense with excellent contrast relative to surrounding tissues. This technique, not requiring contrast administration, also would allow measuring the total volume of thrombi [95]. MRI is also useful in showing the parenchymal lesions secondary to venous occlusion. Parenchymal brain lesions include brain swelling, edema, or venous infarction, which appear as hypointense or isointense on T1-weighted MRI, and hyperintense on T2-weighted MRI; hemorrhagic venous infarcts appear as hyperintense lesions on both MRI sequences. DWI abnormalities consistent with acute infarction may occur, but less prominently compared with arterial infarction [96].

**MR venography**

Several methods can assess venous or dural sinus flow: unenhanced 2D time-of-flight (TOF) MR venography, 3D TOF MR venography, contrast enhancement MR venography, and phase-contrast MR venography [97]. The 2D TOF MR venography is the most commonly used method for the diagnosis of CVT, which typically demonstrates the absence of flow in the thrombosed vessel (*figures 6 and 7*). Contrast-enhanced MR venography is more sensitive than TOF MR Venography.
MR venography has several limitations and potential pitfalls in the diagnosis of cortical vein thrombosis, of partial sinus occlusion, and in distinction between hypoplasia and thrombosis. Reliance on other MR sequences, such as T2* gradient-echo or SWI may surpass the limitation of cortical vein thrombosis diagnosis [94]. The use of contrast may help in other situations. For example, a thrombosed hypoplastic sinus will have marked enhanced sinus signal and no flow on 2D TOF venography; a non-thrombosed hypoplastic sinus will not present abnormal low signal in T2* gradient-echo or SWI.

**Computed tomography–CT venography**

There are patients with contra-indications to perform MRI and in some hospitals, the access to MRI is limited. Therefore, computed tomography (CT) associated with CT venography can be an alternative technique to diagnose CVT.

In the emergency setting, CT is often performed, and is useful to rule out acute or subacute cerebral disorders that may mimic CVT, such as tumor, subdural hematoma, and abscess. CT is normal in up to 30% of cases of CVT, and most of the findings are non-specific. Classic direct signs of CVT are present in about one third of cases, and refers to the visualization of thrombus (figure 9): the cord sign (thrombosed cortical or deep vein), the dense triangle sign (visualization of the clot inside the sinus), and the empty delta sign, visible after injection of a contrast agent as a contrast between the non-opacified thrombus inside the sinus and the collateral veins of the sinus wall [2]. A recent study reported interesting results on the diagnostic accuracy of

**Figure 6**

Magnetic resonance imaging in combination with magnetic resonance venography confirm right sigmoid sinus occlusion in a patient with acute headache. A. Enhanced MRI T1-weighted image shows an isointense signal inside the sigmoid sinus corresponding to a non-opacified thrombus (arrow). B. TOF MR venography typically demonstrates the absence of flow in the corresponding part of the thrombosed sinus (arrow). C. Three months later, an almost complete recanalization of the sigmoid sinus is observed in the MR venography.
non-enhanced CT suggesting that measurement of the venous sinus attenuation can increase the sensitivity of this examination in the diagnosis of acute CVT [98].

Brain CT may show indirect signs of CVT: focal or diffuse white matter hypodensity, hemorrhagic lesions, small ventricles, dilated transcerebral veins intense, and contrast enhancement of falk and tentorium. Parenchymal anomalies occur in 60–80% of cases and some patterns are highly evocative of CVT, such as multiple bilateral lesions, bilateral thalamic edema, temporo-occipital lesions, small juxtacortical hemorrhages [99], or convexity subarachnoid hemorrhage.

CT venography, readily available after brain CT, can confirm the diagnosis of CVT showing filling defects in the dural sinus and cortical veins, sinus wall enhancement, and increased collateral venous drainage [100,101].

CT/CT venography has some advantages over MR: rapid image acquisition, fewer motion artifacts, no contraindication to patients with ferromagnetic devices, and easier to be used in patients with claustrophobia [102]. Additionally, CT venography may be superior in imaging sinuses or cerebral veins with low flow [101]. Some limitations of CT/CT venography are difficult visualization of skull base structures in three-dimensional display, low resolution for small parenchymal lesions, poor detection of cortical and deep venous thrombosis, the risk of contrast reactions, radiation exposure and risk of iodinated contrast nephropathy (e.g., in patients with diabetes, renal failure) which may limit its use in pregnant women, children, and patients with renal failure [101,102].

**Intra-arterial angiography**

Intra-arterial angiography has a spatial resolution superior to CT or MR venography but is currently rarely performed. It is reserved to cases with inconclusive or contradictory findings in the other imaging modalities, to exclude a dural arteriovenous fistula, or when therapeutic intervention is planned.
Typical signs of CVT on angiography are partial or complete lack of filling of veins or sinuses, delayed emptying, dilated collaterals, and the sudden stopping of cortical veins surrounded by dilated and tortuous collateral "corkscrew veins". Anatomic variations may limit the interpretation of angiography, such as hypoplasia of the anterior part of the superior sagittal sinus, duplication of the superior sagittal sinus, and hypoplasia or aplasia of the transverse sinuses [2].

**Laboratory tests**

Besides imaging, there is no confirmatory laboratory test that can confidently rule out acute CVT [87]. Elevated d-dimers support the diagnosis of CVT. A systematic review collected 14 published studies that had assess the value of d-dimers in the diagnosis of 1134 CVT patients [103]. d-Dimer accuracy was good, with a sensitivity of 94% and specificity of 90%. However, false negative d-dimer occurred in patients with
isolated headache, longer duration of symptoms, and limited sinus involvement [103]. In consequence, a normal d-dimer level cannot rule out the diagnosis, and measurement of plasma d-dimer level is not a good screening test in patients with suspected CVT.

**Prognosis**

Cerebral venous thrombosis usually has a good prognosis, but can result in death or permanent disability.

Clinical course is unpredictably in the first days after diagnosis. About one-fourth of CVT patients experience a neurological worsening presenting depressed consciousness, mental status disorder, new seizure, worsening of or a new focal deficit, increase in headache intensity, or visual loss. Patients with depressed consciousness on admission are more likely to dete-riorate. Seizures are more likely to recur in those with seizures at onset and to occur de novo in patients with parenchymal lesions. About one third of patients with neurological deterioration will have new parenchymal lesions if neuroimaging is repeated [33].

Approximately 5% of patients die in the acute phase of the disorder [33,104]. The main cause of death with acute CVT is transtentorial herniation secondary to a large hemorrhagic lesion, followed by herniation due to multiple lesions or to diffuse brain edema. Status epilepticus, medical complications, and pulmonary embolism are among the other causes of early death [105,106]. Deaths after the acute phase are mainly due to the underlying conditions, in particular malignancies or to fatal bleeding related to prolonged anticoagulant treatment.

In a meta-analysis that included prospective and retrospective studies [107], the overall rate of acute death was 5.6%, of death at the end of follow-up was 9.4% and of complete recovery was 88%. In the ISCVT study, the following factors were associated with poor outcome: age more than 37 years, male gender, Glasgow Coma Scale score < 9 on admission, mental status disorder, thrombosis of the deep cerebral venous system, intracranial hemorrhage on admission CT/MRI, malignancy, and infection of the central nervous system [33]. This predictive model was validated in two independent validation cohorts [108]. A risk score was derived from this model: coma, malignancy, and thrombosis of the deep venous cerebral system, scoring 2 points each; mental status disturbance, intracerebral hemorrhage and male gender, scoring 1 point each. A total score of ≥ 3 points indicates a higher risk of unfavorable outcome [108].

Patients presenting with the isolated intracranial hypertension syndrome usually have excellent outcome, more than 90% achieving a complete recovery [33,109]. Among CVT patients who have hemorrhagic lesions at the admission, 21% were dead or dependent at 6 months [33]. In a national multicenter study, including 114 patients with a severe CVT (GCS < 9) admitted to intensive care units, at last follow-up (median 2.5 years), 21% had moderate or severe disability and 34% had died [77]. The same rate of death was described in a monocentric cohort of 41 consecutive severe CVT patients admitted in a French intensive care unit tertiary hospital, although good recovery was attained by the great majority of survivors [78].

Prognosis is less favorable in patients at both extremes of age. The analysis of the ISCVT cohort found that the prognosis in patients older than 64 years is considerably worse than that in younger patients [79]. Only 47% of elderly patients made a complete recovery, whereas 27% died and 22% were dependent at the last follow-up. In children, the death, dependency, and late complication rates are also higher than those in adults. The death rate ranges from 2 to 13% [11,110–112], especially in neonates, whose mortality may be as high as 25% [111]. Only 22% of neonates survive free of any impairment [113].

Concerning the role of recanalization and increased collateralization in the outcome and recovery from CVT, a significant univariate association between clinical outcome and recanalization in patients with CVT was shown in a recent systematic review [43]. No impact of baseline intracranial venous collaterals on the type of brain damage, clinical manifestations or prognosis of patients with CVT was shown in a retrospective cohort study [44].

Patients who survive the acute phase of CVT are at risk for complications, such as further venous thrombotic events, seizures, and headaches. Headaches severe enough to require bed rest or hospital admission afflict 14% of patients with CVT [33]. Although rare, recurrent CVT is one of the causes of severe headache. It is useful to have MRI/MR venography at 3 to 6 months after the venous thrombosis to document the extent of recanalization. If new symptoms occur, suggesting recurrence of CVT, MR and MR venography should be repeated and the images compared with previous ones. Other thrombotic events, namely deep venous thrombosis of the limbs or pelvis and pulmonary embolism occur in about 5% of the patients. Male gender, myeloproliferative neoplasm and severe thrombophilia are associated with a higher risk of recurrent venous thrombotic events [114–116]. The rate of further venous thrombotic events is similar in children [112]. Non-administration of anticoagulant, persistent venous occlusion and presence of prothrombin G20210A mutation were independently associated with recurrent cerebral and systemic venous thrombosis in children [112]. Seizures may occur in up to 11% of the patients. Risk factors for these remote seizures are seizures during the acute phase, a hemorrhagic supratentorial parenchymal lesion or a motor defi-cit [117].

Severe visual loss due to intracranial hypertension is very rare [33,118]. However, a few CVT survivors may be found to have subnormal visual acuity or visual fields as well as esodeviation [118]. Despite apparently good recovery, many patients report residual symptoms. Psychological and cognitive complaints are common
among CVT survivors [119-121]. About half of the survivors of CVT feel depressed or anxious and demonstrate minor cognitive or language deficits, and a substantial proportion remained unable to return to working life [120,122].

**Treatment**

Management of CVT includes acute treatment and post-acute prevention or treatment of CVT complications. In each of these two temporal phases, comprehensive management should consider:

- treatment of the associated conditions/risk factors;
- antithrombotic treatment;
- symptomatic treatment;
- prevention/treatment of complications;
- counseling on healthy lifestyle and future health conditions.

There are both European and American guidelines for the management of CVT [123]. A new version of the ESO CVT guidelines prepared following the GRADE methodology will be available in 2016. Due to lack of randomized clinical trials, most of the recommendations are based on evidence from observational studies (table I).

**Acute treatment**

**Treatment of the associated conditions/risk factors**

Antibiotic treatment is mandatory whenever there is sepsis, meningitis, or other intracranial infection or an infection of a neighboring structure, such as otitis, mastoiditis, or skin infection. For some associated diseases, such as Behçet's disease, vasculitis or other inflammatory conditions, treatment with steroids may be necessary. Any cancer should be managed as recommended, considering that some chemotherapeutic agents have a procoagulant effect and may cause CVT (e.g. l-asparaginase) [124].

**Antithrombotic treatment**

**Anticoagulation**

The recommended antithrombotic treatment in the acute phase is heparin (either IV non-fractionated IV heparin [UFH] or subcutaneous low molecular weight heparin [LMWH], followed by oral anticoagulation with vitamin K antagonists [VKA]).

Heparins are supposed to act by preventing thrombus propagation from one sinus to the next and in particular to the bridging vein, whose thrombosis is the main cause of venous infarcts. Heparins also prevent pulmonary embolism, which is a rare cause of death in acute CVT patients. They may also increase the chances of recanalization, although this is not yet proved neither by observational or intervention studies. The use of heparin in acute CVT is supported by four clinical trials [125]. Two of these trials have major limitations: one used only CT to confirm the diagnosis of CVT and the results of the other were only published in abstract. The meta-analysis of the two other trials [126,127] including 79 patients showed a non-significant relative risk reduction of 0.33 (95% CI 0.08-1.21) for death and 0.46 (95% CI 0.16-1.31) of death or dependency after anticoagulant therapy as compared to placebo. If the two excluded trials were included, the relative risk of death would be 0.33 and significant (95% CI 0.14–0.78) [125].

An important question is the safety of anticoagulation in CVT patients with intracerebral hemorrhages. Thirty-four of 79 patients (43%) include in the Berlin and Dutch trials had an intracerebral hemorrhage at prior to randomization. None of the patients randomized to heparin developed a new intracerebral hemorrhage, in contrast to 3 patients allocated to placebo. Only one of the new intracerebral bleedings occurred in patients who have a hemorrhage prior to randomization [125].

Several observational series showed that the heparin is safe and can be used in acute CVT patients with intracranial hemorrhagic lesions. However, new observational follow-up imaging studies are needed to assess more confidently the risk of new intracranial bleeding in acute CVT patients treated with UFH/LMWH.

Another important question is the choice between UFH and LMWH. LMWH has several advantages, except for the cost. Thrombocytopenia occurs much more commonly with IV heparin. LMWHs have longer half-life, more predictable clinical response and less interaction with platelets compared with standard heparin. Two small trials with methodological problems [128,129] and one observational study [130] suggest that LMWH is at least equally effective and possibly superior to IV heparin for the treatment of CVT, with a lower risk of bleeding.

If lumbar puncture or other invasive interventions or surgery are planned to be performed, it is preferable to opt for UFH, due to its shorter half-life. If the patient is on UFH, heparin should be stopped 4–6 hours before the procedure in order to have a return to normal values of the activated partial thromboplastin time (APTT). If the patient is on LMWH, this medication should be stopped 12 hours before the procedure. UFH or LMWH can be restarted immediately after lumbar puncture or other procedures with low bleeding risk and after 12-24 h, depending on the inherent bleeding risk, after major procedures (24 h for neurosurgery).

**Endovascular thrombolysis**

The majority of acute CVT patients have a very favorable clinical course and outcome on anticoagulant treatment. However, a few patients continue to deteriorate or do not improve despite anticoagulation, while a few other present acutely in a very severe clinical condition [77] and need an escalation of the treatment plan. Direct endovascular thrombolysis, aiming to dissolve the venous clot and reopen the occluded sinus or vein, is an upgrade to heparin in severe cases or in patients who fail to improve or deteriorate despite anticoagulation. Catheterization of the sigmoid, transverse, and superior sagittal sinus via the femoral venous or jugular approach is followed by local injection of recombinant tissue plasminogen activator (tPA) or urokinase. Mechanical thrombectomy by disruption (guiding catheter),
removal (balloon catheter), or suction (rheolytic catheter) may also be performed. No randomized trials of endovascular treatment for sinus thrombosis have been performed, but multiple case series claiming good results have been published. A systematic review of 15 studies including 156 patients revealed that despite this treatment there is a death rate of 9% and that local thrombolysis is complicated by a non-negligible rate of 10% major bleeding, including 8% intracranial hemorrhages, 58% of which were fatal [131]. A systematic review of 185 patients treated with thrombectomy, of whom 47% were in stupor or coma, revealed a very high recanalization rate (95%, 21% partial), a 10% rate of new or increasing intracerebral hemorrhage, 84% good outcome and 22% deaths. This indicates that thrombectomy in severe CVT patients is feasible and safe, but a definite answer on its efficacy and safety and on whose patients benefit more from this intervention needs a controlled study [132]. A randomized trial to compare endovascular treatment (thrombolysis/thrombectomy) versus heparin in acute CVT patients with at least one risk factor for unfavorable outcome (thrombolysis or anticoagulation for cerebral venous thrombosis – TO-ACT) is currently ongoing [133]. Until this trial is completed, endovascular thrombolysis should be considered a

### Table II

**Interventions to treat cerebral venous thrombosis: source and quality of evidence**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Quality of evidence</th>
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<tbody>
<tr>
<td></td>
<td>Observational</td>
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<tr>
<td><strong>Acute phase</strong></td>
<td></td>
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<tr>
<td>Heparin</td>
<td>Yes</td>
</tr>
<tr>
<td>UFH vs. LMWH</td>
<td>Yes</td>
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<tr>
<td>IV thrombolysis</td>
<td>Yes</td>
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<tr>
<td>Endovascular thrombolysis</td>
<td>Yes</td>
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<tr>
<td>Thrombectomy</td>
<td>Yes</td>
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<tr>
<td>Lumbar puncture</td>
<td>Yes</td>
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<tr>
<td>Acetazolamide</td>
<td>Yes</td>
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<tr>
<td>Steroids</td>
<td>Yes</td>
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<tr>
<td>Osmotherapy</td>
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<tr>
<td>Shunting</td>
<td>Yes</td>
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<tr>
<td>Decompressive surgery</td>
<td>Yes</td>
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<tr>
<td>Anti-epileptic drugs</td>
<td>Yes</td>
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<tr>
<td><strong>Post-acute phase</strong></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulants, VKA</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral anticoagulants, duration</td>
<td>Yes</td>
</tr>
<tr>
<td>NOACs</td>
<td>Yes</td>
</tr>
<tr>
<td>LMWH during pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Yes</td>
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<tr>
<td>Acetazolamide</td>
<td>Yes</td>
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<tr>
<td>Topiramate</td>
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<tr>
<td>Shunting</td>
<td>Yes</td>
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<tr>
<td>Sinus stenting</td>
<td>Yes</td>
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<tr>
<td>Optic nerve sheat fenestration</td>
<td>Yes</td>
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<tr>
<td>Anti-epileptics</td>
<td>Yes</td>
</tr>
</tbody>
</table>

UFH: unfractionated heparin; LMWH: low molecular weigh heparin; VKA: vitamin K antagonist; NOAC: new oral anticoagulant.

1 These studies were performed in patients with idiopathic intracranial hypertension not in patients with intracranial hypertension secondary to cerebral venous thrombosis.
treatment option for CVT patients who worsen despite anticoagulant therapy, in particular those with thrombosis of the cerebral deep venous system and without large hemispheric lesions with mass effect and imminent risk of herniation.

**Treatment of intracranial hypertension**

In patients presenting a syndrome of isolated increased intracranial pressure (ICP), with severe headache and papilledema, intracranial hypertension can be reduced and symptoms rapidly relieved through a therapeutic lumbar puncture, which can be performed safely [134]. Diuretics, which inhibit carbonic anhydrase and therefore reduce CSF production, such as acetazolamide or topiramate are often used with the aim of reducing intracranial pressure to ameliorate headache and prevent visual damage [135]. A case-control observational study failed to demonstrate any effect of acetazolamide on functional outcome or death [136]. Corticosteroids have a potential to reduce vasogenic edema, but also have a prothrombotic action. A case-control comparative observational study showed that corticosteroid do not improve outcome in the acute phase of CVT [137]. Corticosteroids should only be used to treat an inflammatory associated condition (e.g. Behçet’s syndrome, vasculitis) [138-140].

Comatose patients should be admitted to an intensive care unit for intubation, sedation, mechanical ventilation and ICP monitoring. Osmotherapy (e.g. mannitol) is then used in bolus to reduce ICP. Decompressive surgery is used to prevent fatal herniation in comatose patients with large parenchymal lesions and impending herniation. In fact, herniation due to unilateral mass effect is the major cause of death in CVT [141]. In CVT patients with large parenchymal lesions and impending herniation several single center series [142-147] and one multicenter registry and systematic review of individual operated patients [148].

Lath et al. [143] showed that decompressive surgery (hemicraniecotony or hematoma drainage) is lifesaving and often results in good functional outcome, irrespective of age, coma, aphasia, bilateral lesions, or bilateral fixed pupils. Concerning the role of shunting alone to reduce intracranial pressure in acute CVT, a systematic review showed that shunting alone does not prevent death or unfavourable outcome [149]. Except in the rare occurrence of symptomatic hydrocephalus [150], ventriculostomy, or ventriculoperitoneal shunts are not useful in acute CVT and should not be used as an alternative to decompressive surgery.

**Treatment and prevention of early seizures**

Early seizures are defined as those, which occur within 2 weeks of the diagnosis of CVT. Risk factors for early seizures, are seizures before or at admission and supratentorial lesions, especially if hemorrhagic. The risk is higher in patients with both risk factors. Concerning the prescription of prophylactic anti-epileptic drugs (AED), there are no randomized controlled studies. Four observational studies were published, two prospective [151,152] and two retrospective [153,154] comparing CVT patients receiving or not AED [152] found a risk reduction of early seizures in patients with supratentorial lesions who previously had seizures with an OR = 0.006, but without no influence on outcome (death or dependency). Patients with supratentorial lesion and a seizure (before, at or after admission) should be given AED to prevent further seizures. AED may also be considered in patients with a single seizure in the absence of parenchymal lesions.

Patients in status epilepticus, generalized or partial, should be treated accordingly to the guidelines for the treatment of epileptic status. If available, IV levetiracetam is a good option for seizure control, because of its safety profile and lack of interactions with anticoagulants.

**Prevention and treatment of post-acute complications**

**Recurrent cerebral venous thrombosis and other thrombotic events**

The risk of all venous thrombotic events after the initial CVT is 4.1 per 100 person years and the rate of recurrence of CVT is 1.5 per 100 person years [114]. This risk is similar to that observed after lower extremity deep venous thrombosis (DVT) [155]. Therefore, oral anticoagulation with warfarin or other vitamin K antagonists (VKA) is recommended after the acute phase of CVT to prevent further venous thrombotic events, including the recurrence of CVT. In adults, risk factors for recurrence of cerebral venous thrombosis are male gender, myeloproliferative diseases (polycythemia vera or essential thrombocythemia) and severe thrombophilia, such as antiphospholipid syndrome and deficiencies of natural anticoagulants (antithrombin, protein C and protein S) or combined thrombophilic defects [114-116]. Such risk does not appear to be increased in mild thrombophilia, such as in heterozygotes for gain of function mutations on coagulation proteins (factor V Leiden and prothrombin 20210GA mutations). Optimal duration of anticoagulation has not yet been addressed in randomized controlled trials. Such a study (Extend-Ing Oral Anticoagulant treatment after acute Cerebral Vein Thrombosis, EXCOA-CVT www.excoa-cvt.com) is currently including patients. Meanwhile, oral anticoagulation is usually maintained for 3–12 months after acute CVT, aiming at an international normalized ratio of 2–3, depending on the inherent individual thrombotic risk. American guidelines suggest that if CVT is related to a transient risk factor, anticoagulants are to be used for a shorter period (3–6 months), while in idiopathic CVT associated with ‘mild’ thrombophilia, they should be used for a longer period (6–12 months) and in patients with ‘severe’ thrombophilia or recurrent CVT or CVT followed by DVT or vice-versa, anticoagulants for life may be considered.

In a few case reports and two small cases series [156,157], new direct oral anticoagulants (dabigatran, rivaroxaban) were used...
in CVT patients instead of vitamin K antagonists. New oral anticoagulants have some practical advantages and are probably safer but until more evidence is available they should not be used routinely, and be reserved for patients with intolerance or complications while on warfarin or other VKA, or when the target INR is difficult to achieve or maintain. A pilot randomized clinical trial comparing dabigatran with warfarin will be launched in the last trimester of 2016.

**Headache**

Headache is a common complaint during the follow-up of CVT patients. In general, headaches are primary headaches, of tension type or migraine, not related to CVT. In patients with persistent or severe headaches, imaging (MR with veno-MR or veno CT) must be repeated to rule out or confirm recurrent CVT and compared with previous exams. Partial recanalization can lead to stenosis of a previously occluded sinus, but clinical significance of such stenosis is not known.

If headache persists despite normal neuroimaging results, a diagnostic and therapeutic lumbar puncture may be needed to exclude and treat elevated ICP. In patients with a persistent syndrome of isolated increased ICP, therapeutic options include weight loss, acetazolamide or topiramate, repeated lumbar punctures and exceptionally stenting of the transverse sinus [158] or lumbo-peritoneal shunt [159,160]. Special care should be taken to prevent severe visual loss, which is rare nowadays. Patients with papilledema or visual complaints should have a complete neuro-ophthalmological evaluation including visual acuity and visual field testing. Rapid diagnosis of CVT and treatment of intracranial hypertension are the main measures to prevent visual loss. Surgical fenestration of the optic nerve sheath [161] can be performed as a rescue intervention to prevent visual loss in centers with experience in this procedure.

**Treatment and prevention of seizures**

Remote seizures those occurring more than 2 weeks after the diagnosis of CVT affect 5–32% of patients. Most of these seizures occur in the first year of follow-up. Risk factors for remote seizures are an early seizure, a supratentorial and hemorrhagic lesion on admission CT/MR, and paresis [117]. Prophylactic antiepileptics for a defined duration (usually 1 year) can be prescribed in patients with an early seizure and parenchymal lesion(s). It may also be considered in patients with single seizure in the absence of parenchymal lesions.

**Contraception and future pregnancies**

Oral contraception and hormonal replacement therapy, except for those containing only progestogens, should be stopped. Emergency contraception is also contraindicated. Contraceptive methods other than oral or parental contraceptives should be used. CVT and pregnancy or puerperium-related CVT are not a contraindication for future pregnancy. Although pregnancy and the puerperium are the risk factors for CVT, the absolute risk of complications during subsequent pregnancy among women who have a history of CVT is low. In a recent systematic review of 13 studies, only 1 CVT recurrence in 217 pregnancies (0.9%) and 5 non cerebral venous thrombotic events in 186 pregnancies (2.7%) were detected. However, the relative risks are higher than in control populations. The rate of miscarriage is not different from that of the general population [43]. Although the evidence is very weak, women with previous CVT may be advised to consider using prophylactic LMWH during pregnancy and puerperium. CVT occurring during pregnancy or puerperium should be preferentially treated with LMWH and this treatment should be continued for at least 6 weeks postpartum. Warfarin is teratogenic and should not be given in the first trimester of pregnancy. Oral anticoagulants may also induce fetal or placental hemorrhage, mainly in the last trimester of pregnancy and at delivery, because they cross the placenta.

**Unmet needs and future directions**

In the last decade, there was considerable progress in the definition of the natural history of CVT and on the identification of predictors of relevant health outcome for CVT patients. These advances were possible due to large multicenter collaborations, leading to samples of several hundred patients. Analysis of particular subgroups could also be performed in these cohorts. However, a number of critical clinical points and unmet needs (digits) still remain to be answered (letters), namely:

- the diagnosis is frequently delayed or missed at the 1st medical encounter;
- a valid diagnostic biomarker (other than imaging) should be identified or developed;
- new/improved MR sequences should be designed to increase current diagnostic pitfalls and simplify/reduce the cost of confirming the diagnosis of CVT by neuroimaging;
- only a few subjects who are exposed to the risk factors/associated conditions develop CVT;
- the efficacy and safety of almost all therapeutic interventions in the acute or post-acute phases of CVT are supported by low or very low quality evidence:
- observational (large multicenter registries, administrative data review) and experimental studies (randomized clinical trials) to evaluate the efficacy and safety of all interventions and to identify the patients who most/less benefit from them;
- the information on psychosocial outcomes and its predictors is insufficient and of questionable quality:
- large cohort or cross-sectional multicenter studies using validated, commonly accepted instruments (available in different centers and languages) to measure psychosocial outcomes.
Due to the low incidence of CVT, multicenter academic collaboration is a key element to improve our knowledge on CVT. Indeed single centers studies are always underpowered and prone to selection bias. Industry is unlikely to support experimental studies in CVT due to the relatively low prevalence of CVT. In the next few years, numerous observational studies and treatment trials on several uncertain issues (e.g. safety of heparin in the acute phase, endovascular thrombolysis/thrombectomy, duration of anticoagulation, NOACs, decompressive surgery, pregnancy after CVT) will increase the level of evidence that currently supports the management of CVT and will help to select the most appropriate treatment to the CVT patients who will benefit most from it.

Disclosure of interest: the authors declare that they have no competing interest.

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