Journal of Thrombosis and Haemostasis, **16**: 1918–1931 DOI: 10.1111/jth.14210

REVIEW ARTICLE

Cerebral venous sinus thrombosis

M. CAPECCHI, M. ABBATTISTA and I. MARTINELLI
A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

To cite this article: Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. *J Thromb Haemost* 2018; **16**: 1918–31.

Summary. The cerebral venous system is an unusual site of thrombosis, with a particularly high incidence in young adults. This incidence has increased in past decades because of the improvement of neuroradiological techniques. Risk factors for cerebral venous sinus thrombosis overlap with those of other venous thromboembolism sites; however, some are specific for this particular anatomical district. Prognosis is favorable in most cases if diagnosis is made rapidly and treatment is promptly initiated, even if acute complications or chronic invalidity still occur in a quarter of patients. The mainstay of treatment is anticoagulation, which is necessary in order to block clot propagation and obtain recanalization. Intracranial bleeding does not contraindicate anticoagulation. Endovascular procedures are reserved for patients with a particularly severe presentation or rapidly declining neurological symptoms despite appropriate anticoagulation, although data from clinical trials are lacking. Specifically, this review addresses the epidemiology, clinical presentation and course, risk factors, and treatment of cerebral venous sinus thrombosis, with a special focus on the pediatric population.

Keywords: anticoagulants; cerebral hemorrhage; intracranial thrombosis; low-molecular-weight heparin; sinus thrombosis; venous thromboembolism.

Anatomy

The cerebral venous system can be divided into two major compartments considering the anatomic and functional characteristics of the blood vessels: the cerebral veins and the dural venous sinuses (Fig. 1). Considering the topographic distribution, a superficial and a deep system can be distinguished. The superficial system drains blood from the cerebral cortex mainly into the superior sagittal sinus, which in turn drains into the transverse sinuses. The deep system drains blood from the deep white matter and the basal ganglia to the inferior sagittal sinus, that continues into the straight sinus and then into the transverse sinuses. From the transverse and the straight sinuses blood flows out of the sigmoid sinuses, passing through the sinus confluence (torcular Herophili), and finally into the internal jugular veins. Many anastomoses exist between the cerebral veins from the fetal period onwards. The dural venous sinuses are delimited by the superficial (periosteal) and the deep (meningeal) layer of the dura mater and their walls are composed of only the dura mater layer lined with endothelium, hence lacking the tunica media. Additionally, these sinuses lack valves. Dural venous sinuses drain blood from the cerebral veins and the cerebrospinal fluid from the subarachnoid space, via the arachnoid Pacchionian granulations, which are present particularly in the superior sagittal sinus. The classic anatomy varies considerably among individuals and the knowledge of such variations is essential for a correct interpretation of radiological images. The most frequent anatomic variants are: asymmetries of transverse sinuses, observed in nearly 50% of patients; hypo-/aplasia of all or part of the transverse sinuses, observed in nearly 20% of patients; and less frequently hypo-/aplasia of the frontal part of the superior sagittal sinus [1].

Pathophysiology

The formation of a thrombus in the cerebral venous circulation leads to an increase in the hydrostatic pressure in the veins and capillaries upstream of the occlusion. However, because of the anastomotic circuit of the cerebral venous system, the increased venous pressure is usually compensated to some extent. If the increase in the venous pressure overcomes the compensation capacity the following can occur: blood–brain barrier disruption, extravasation of fluids into the cerebral parenchyma and consequent localized edema. Furthermore, if the venous pressure exceeds the arterial pressure, a reduction of

Correspondence: Ida Martinelli, A.Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milan, Italy
Tel.: +39 02 5503 5468
E-mail: ida.martinelli@policlinico.mi.it

Received: 29 March 2018
Manuscript handled by: F. R. Rosendaal
Final decision: F. R. Rosendaal, 5 June 2018

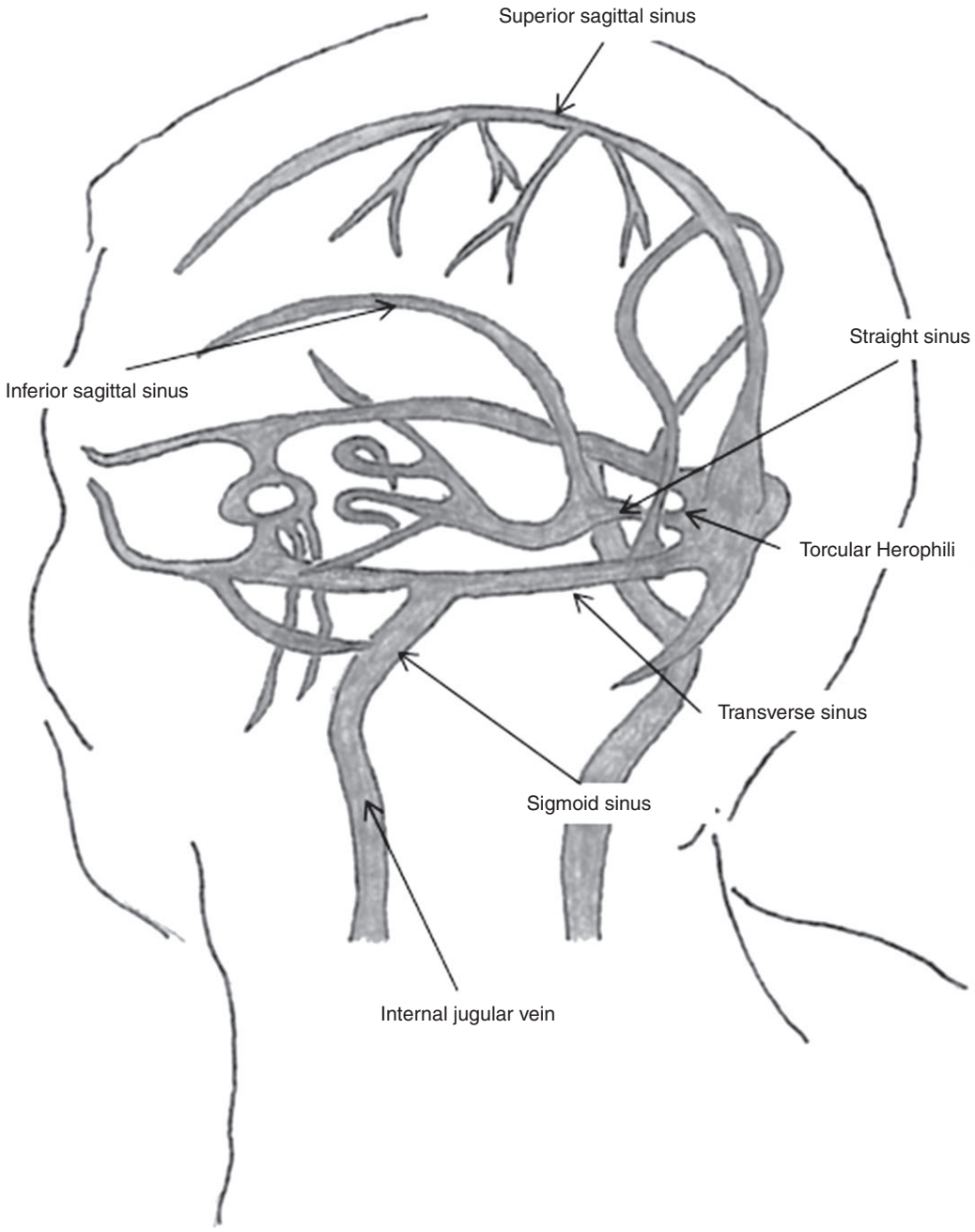

Fig. 1. Anatomy of the cerebral venous system.

arterial flow and consequent arterial ischemia can occur and, if not adequately treated, it may progress to hemorrhagic infarction [2]. A peculiar characteristic that distinguishes vasogenic (due to venous occlusion) from cytotoxic (due to arterial occlusion) edema, is that in the former the perfusion pressure is not usually reduced and therefore irreversible brain tissue damage is unlikely. Indeed, in venous stroke a resolution of thrombi and a favorable prognosis are more likely than in arterial stroke. The peculiarity of venous occlusion is the reduction of cerebrospinal fluid reabsorption, by reducing cerebrospinal fluid access to the arachnoidal Pacchionian granulations, leading to intracranial hypertension [3]. This scenario is more frequent with superior sagittal sinus occlusion (where arachnoidal Pacchionian granulations are present), but can also occur in the occlusion of other sinuses.

Epidemiology

Cerebral venous sinus thrombosis (CVST) is a rare manifestation of thrombosis with an incidence that varies

between studies. In adults, the annual incidence of CVST is two to five cases per million individuals [3,4], but it is likely to be underestimated because of the lack of well-designed epidemiological studies. Two recent studies in the Netherlands and southern Australia found a higher incidence than previously reported of 13.2 and 15.7 annual cases per million, respectively [5,6]. The high prevalence of infection-related CVST can result in even higher figures in others countries (18% in Pakistan), but the exact incidence among different ethnic groups is pending investigation [7–9]. At variance with arterial stroke that is more prevalent in the elderly, CVST typically affects young adults with a mean age of 35 years and is more common in women than in men (2.2:1) because of sex-specific risk factors [10]. The superior sagittal and the transverses are the most frequently involved sinuses (60% of patients), followed by the internal jugular and cortical veins (20%). In almost two-thirds of patients CVST involves more than one sinus.

Epidemiology in children and neonates

The annual incidence of CVST in the pediatric population is approximately seven cases per million and is higher in neonates than in children [11–14]. The sex ratio seems balanced because of the absence of sex-specific risk factors [12]. Similarly to adults, the superficial sinuses are the most frequently involved (particularly the superior sagittal and the transverse sinuses) and the transverse sinuses are more frequently involved in children older than 2 years of age (60% vs. 39%) [11,15].

Clinical presentation

Because symptoms of CVST are variable and aspecific, diagnosis is often delayed to a median period of 7 days from the onset of clinical manifestations [16]. The International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVT), which included 624 patients, described the following as the most common presenting symptoms: headache (88.8%), seizures (39.3%), paresis (37.2%), papilledema (28.3%) and mental status changes (22%) [16].

Headache is usually the first symptom at onset of CVST. In only 10% of cases does the headache have a thunderclap outbreak, mimicking a subarachnoid hemorrhage [17]. Because of its aspecific nature, physicians must have a high suspicion of CVST when dealing with a new onset and progressively increasing intensity of headache, which is the only presenting symptom in about 32% of patients [17]. The location of the headache is not informative as it does not correlate with the thrombosis site. The absence of headache is typical of elderly patients, especially men [18], and in those with cortical vein thrombosis who have normal cerebrospinal fluid homeostasis. The pathophysiologic mechanism of headache in CVST is the increase in intracranial pressure due to reduced cerebrospinal fluid reabsorption. For this reason, the intensity of the headache typically increases when patients lie down and after the Valsalva maneuver. For reasons not yet fully understood, headache is more common in patients with CVST than in those with arterial stroke (25% of cases) [19].

Seizures are focal in one quarter of patients, in another quarter they begin as focal and then generalize and in the remaining half, seizures are generalized *ab initio*[20]. Seizures are more frequent in patients with CVST than in those with arterial stroke (2–9%) [20], perhaps as a consequence of the accumulation of catabolic products due to venous stasis.

Focal neurological deficits such as paresis, dysarthria and aphasia are due to localized damage in the cerebral cortex, secondary to a venous infarction. Focal deficits are more frequent in patients with thrombosis of the superficial system with involvement of the parasagittal cortex, where the motor and sensory areas are located.

Papilledema is the consequence of intracranial hypertension and can cause diplopia and visual loss. Patients with thrombosis of the cavernous sinuses may also develop proptosis, orbital pain, chemosis and ophthalmoplegia secondary to a palsy of the oculomotor (III), trochlear (IV) and abducens (VI) cranial nerves.

Mental status changes such as amnesia, mutism, confusion or delirium are seen in patients with thrombosis of the deep system, particularly those with large venous infarctions or bilateral edema of the basal ganglia and thalami. The most severe cases can have a rapid neurological deterioration, leading to coma and death.

Clinical presentation in children and neonates

In children, symptoms at onset are even more aspecific than in adults and are frequently attributable to more common diseases such as infections or dehydration, making the suspicion and diagnosis of CVST particularly difficult. In general, symptoms in children are the same as in adults, but generalized neurological deficits are more common and seizures are more frequent in neonates [11].

Diagnosis

When CVST is suspected in adults the first-line imaging technique is unenhanced computed tomography (CT) scan; this allows for the ruling out of brain tumors, abscesses or arterial stroke. In the acute phase, CVST is seen in unenhanced CT scans as a hyperdense signal in the vessel lumen, that becomes iso- and then hypodense after the first week. Depending on the location of CVST, two specific radiological signs are described: the 'dense triangle sign' when thrombosis is located in the superior sagittal sinus, and the 'dense cord sign' when located in a cortical or deep vein [3] (Fig. 2A). However, such signs

are rarely described (considering that the unenhanced CT scan has a low sensitivity), resulting positive in only 30% of patients with CVST [21]. The addition of contrast agent increases the sensitivity to 99% for sinus thrombosis and 88% for vein thrombosis, figures similar to those obtained with magnetic resonance imaging (MRI) [22,23]. In the presence of the contrast agent, a specific radiological sign is the 'empty delta sign', a filling defect in the middle of the venous lumen with a peripheral enhancement (Fig. 2B). Advantages of CT scanning are the availability in emergency and the ability to show the presence of local complications associated with CVST, such as subarachnoid or intraparenchymal hemorrhage or cerebral edema. Disadvantages are the exposure to ionizing radiation and the need for contrast agent to increase the accuracy. Currently, MRI is the reference standard imaging technique for diagnosis of CVST, despite the fact that exact sensitivity and specificity are not known because of the lack of proper comparative studies with catheter angiography. Catheter angiography was the historical reference standard technique, which today, due to its invasiveness, is reserved for patients with an inconclusive CT scan and MRI or for candidates undergoing endovascular procedures [24,25]. Maximum accuracy is obtained with the combination of classic MRI sequences, which are able to show the thrombus, together with venography, which can show reduction or absence of flow and therefore distinguish hypoplastic sinuses, partial sinus occlusion, thrombosis of cortical cerebral veins, or filling defects due to hyperplastic arachnoid granulations (Fig. 3) [26]. The advantages of MRI are the absence of both radiation exposure and intravenous contrast agent, and the ability to establish the age of the clot. Finally, when D-dimer is high it increases the likelihood of deep vein thrombosis of the lower limbs or pulmonary embolism; it has been investigated in several studies as a predictive factor for CVST, but has consistently shown a low sensitivity and specificity [27]. Despite this, the ESO guidelines suggest measuring D-dimer before neuroimaging in patients with suspected CVST, except in those with isolated headache and in the case of prolonged duration of symptoms (i.e. > 1 week). The quality of evidence is low and the strength of recommendation is weak [28].

Diagnosis in children and neonates

In children, imaging techniques for diagnosis are the same as in adults, whereas in neonates the first choice is the transfontanellar doppler ultrasound, which has the advantage of being extensively available and non-invasive, albeit strongly operator dependent. In the case of inconclusive results and a persistent clinical suspicion of CVST, enhanced CT scan and MRI must be performed.

Prognosis

For a long time CVST has been considered a life-threatening condition, but the case fatality rate has decreased proportionally over time, from more than 50% to 5–10% [29]. Increased clinical awareness, the advancement of neuroimaging techniques and the improvement in therapeutic management have enabled earlier diagnosis and identification of less severe cases, ensuring a better prognosis. However, data on clinical outcome stem from

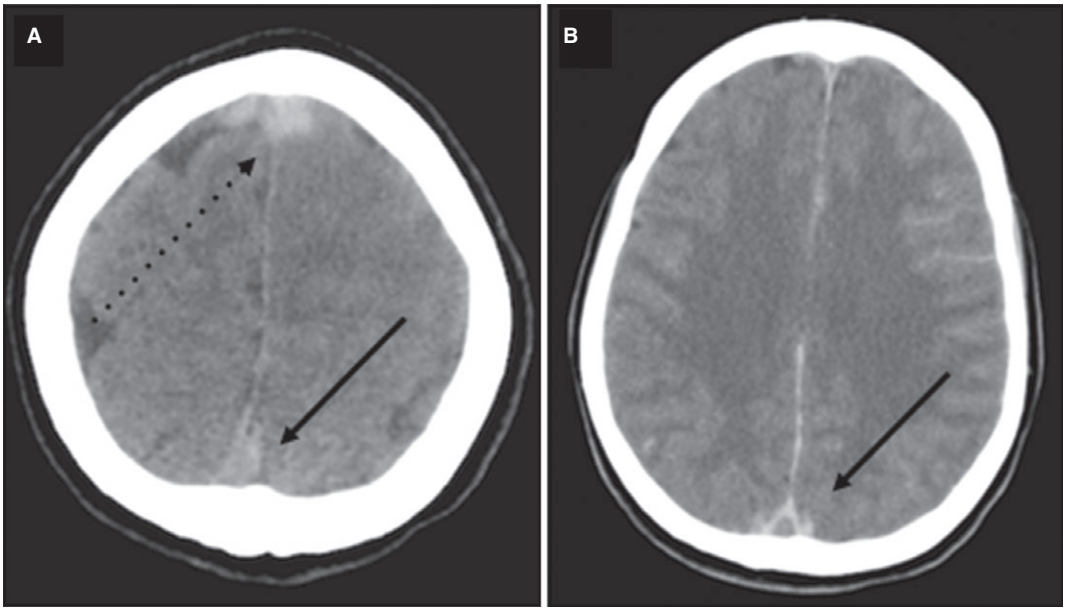

Fig. 2. Superior sagittal sinus thrombosis on computed tomography (CT) scan. (A) Unenhanced CT scan showing the dense triangle sign (arrow) and a peri-thrombotic frontal hemorrhagic suffusion (dashed arrow). (B) Enhanced CT scan showing the empty delta sign (arrow) of the superior sagittal sinus.

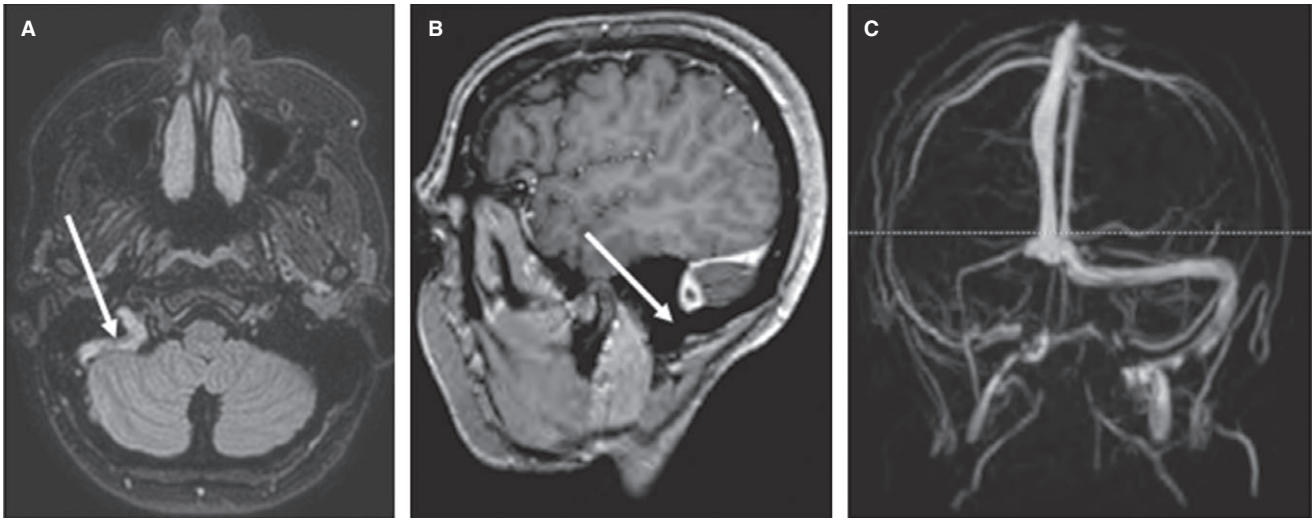

Fig. 3. Cerebral sinus vein thrombosis on magnetic resonance imaging (MRI) sequences. (A) Fluid attenuated inversion recovery axial sequence showing absence of flow-void in the right sigmoid sinus (arrow). (B) Sagittal contrast enhanced T1-weighted sequence showing a partial occlusion of the right sigmoid sinus (arrow). (C) Three-dimensional reconstruction of the cerebral venous system showing the absence of flow in the right transverse and sigmoid sinuses and right internal jugular vein.

studies with small sample sizes, which suffer from methodological heterogeneity and are usually referred for follow-up visits for up to only 12 months. The clinical course of the acute phase is unpredictable and in approximately 5% of patients intracranial hemorrhage followed by herniation, seizures, pulmonary embolism or severe comorbidity can be fatal [16,30,31]. A minority of patients with CVST (15–20%), have different degrees of permanent disability or die [16,32]. A meta-analysis reported an overall mortality of 9.4% (122 deaths among 1303 patients), although the causes of death during follow-up were mainly related to concomitant diseases (e.g. cancer) rather than to CVST itself [30,33]. The majority of patients who recover completely achieve relative independence, usually expressed as between 0 and 2 on the modified Rankin Scale (mRS), although mild residual symptoms, such as headache, motor deficits, linguistic difficulties, and impaired vision or cognition, often remain [16,34–36]. Only 5–10% of patients who survive the acute phase remain moderately or severely dependent (mRS 3 or 4) [16,34]; however, this proportion increases up to 34% in those with massive CVST [37].

Recanalization

To date, few studies with small sample sizes have investigated the recanalization rate of CVST. Differences in the definition of recanalization and time of evaluation across studies make it difficult to pool data and to provide homogenous results. With these limitations, the rate of recanalization (complete or partial) is around 85%, ranging between 73% and 93% [30,38]. Almost 50% of cases achieve a complete recanalization after a median time of 6 months. Recanalization occurs mainly in the first months after CVST and is a dynamic process continuing for up to 12 months, whereas recanalization after 1 year is rare [30,38,39]. A late recanalization has been described in patients with CVST, occurring during hormonal treatment [39]. Controversial and limited data are available regarding the influence of the degree of recanalization on functional outcome [40,41]. One study reported a greater chance of good functional outcome associated with complete recanalization [38], whereas others did not confirm this finding [39,42]. A recent large study including 508 patients showed a high recanalization rate at 3 months after CVST (81%) and an independent association between recanalization and a favorable neurological outcome [43].

Recurrence rate

Data on recurrent venous thrombosis derive mainly from studies with small sample sizes and retrospective design, underpowered to detect potential risk factors for recurrence. The overall incidence of recurrent venous thrombosis within the first year after a first episode of CVST is estimated at around 4 per 100 patient-years (p-y) [44]; that of recurrent CVST is 0.5% to 2.2% p-y and that of recurrent deep vein thrombosis of the lower limbs and/or pulmonary embolism is 1.1% to 5.0% p-y [16,44–47]. Notably, male sex is associated with a 7-fold increased risk of recurrence [44,46]. Cohort studies on long-term evaluation of the risk of recurrent thrombosis after anticoagulant therapy discontinuation showed higher figures in the first period (5.0% p-y, 2.6% p-y and 1.7% p-y in the first, third and tenth year after discontinuation,

respectively) for an overall risk of 2 to 3.5 per 100 p-y [46,47].

Prognosis in children and neonates

The mortality rate varies from 5% to 10% and increases up to 25% in newborns [48]. Few studies have investigated the clinical outcome of neonates and children who survive the acute phase of CVST and no data on their subsequent neurodevelopment are available. The longest observational period was described in a large prospective study that included 104 neonates followed for a median period of 2.5 years (range 6 months to 15 years) [49]. Prognosis in children seems worse than in adults, with 20–70% of patients presenting residual neurological deficits [13,49,50]. In a series of 42 neonates, one died and only 21% of those who completed 2 years of follow-up recovered completely [51]. A European cohort study reported a recanalization rate of 69% (46% complete and 42% partial) between 3 and 6 months after CVST [52], and another recent study found a rate of 85% at 3 months in neonates compared with 56% in children [53]. Despite the limited data, complete recanalization seems to occur earlier in children than in adults, particularly in neonates [53].

The recurrence rate of thrombosis varies between 0% and 20% [15,48–50], with the highest figures in children older than 2 years [11,52]; this is mainly due to underlying systemic diseases (e.g. systemic lupus erythematosus and Behçet disease) [54]. The avoidance of anticoagulant therapy, the lack of recanalization and the presence of the G20210A prothrombin gene mutation have all been associated with an increased risk of recurrence of 11.2-, 4.1- and 4.3-fold, respectively [38,52].

Table 1 Risk factors for cerebral vs. sinus thrombosis

Permanent risk factors	Transient risk factors
Inherited thrombophilia	Sex related
Prothrombin G20210A mutation	Oral contraceptive
Factor V Leiden	Pregnancy
Antithrombin deficiency	Puerperium
Protein C deficiency	Infections
Protein S deficiency	Head and neck infections (e.g. mastoiditis, sinusitis, otitis, osteomyelitis, abscess and meningitis)
Malignancy	Malignancy
Advanced-stage cancer	Cerebral and non-cerebral solid cancer
Systemic diseases	Mechanical
Antiphospholipid syndrome	Head trauma, neurosurgical procedures, lumbar puncture, jugular vein catheterization
Autoimmune diseases (systemic lupus erythematosus, Behçet disease and vasculitis)	Other
Inflammatory bowel diseases	L-asparaginase treatment
Nephrotic syndrome	Severe dehydration
Hematological diseases	Severe anemia
Paroxysmal nocturnal hemoglobinuria	Obesity
Sickle cell disease	Maternal (specific for neonates)
β-thalassemia, myeloproliferative neoplasms	Maternal infections
	Obstetrical trauma
	Obstetrical complications (gestational diabetes, preeclampsia/eclampsia and premature rupture of membranes)

Risk factors

Like any thrombosis, CVST has a multifactorial etiology (Table 1). In 85% of patients at least one risk factor is identified and 50% of events are triggered by the interaction of more risk factors. A small proportion of cases remains idiopathic (i.e. no direct cause or risk factor can be identified) [16,55].

Sex related

CVST is more common in women of reproductive age than in men, as a result of the use of oral contraceptives or hormone replacement therapy, pregnancy and the puerperium [56]. Oral contraceptive use is by far the most common risk factor, reported in more than 80% of women in various series and associated with a pooled estimate of approximately 6-fold increased risk of CVST [57]. A recent case–control study showed that overweight and obesity in women using oral contraceptives further increased the risk of CVST up to 30-fold in a dose-dependent manner [58]. An increase in risk also occurs with the multiplicative interaction between oral contraceptive use and the presence of thrombophilia abnormalities [59,60]. Pregnancy or the puerperium are responsible for 5–20% of CVST, with an incidence of 12 cases per 100 000 deliveries [4,56,61].

Thrombophilia abnormalities

Inherited thrombophilia abnormalities, that is, the common gain-of-function mutations in factor (F) V and FII (FV Leiden and prothrombin G20210A polymorphism) and the rare lack-of-function deficiencies in antithrombin, protein C and protein S, are well-established risk factors for venous thromboembolism, including CVST. Heterozygous FV Leiden or prothrombin polymorphism are reported in 6–24% of patients with CVST, with the latter being more prevalent in several case series [16,62,63]. A recent meta-analysis that included 23 cohort and 33 case–control studies reported a solid risk estimate of CVST for

prothrombin polymorphism (OR, 6.05; 95% CI, 4.12–8.90) and FV Leiden (2.89; 95% CI, 2.10–3.97), and a strong estimate for protein C (OR, 8.35; 95% CI, 2.61–26.67) and protein S (OR, 6.45; 95% CI, 1.89–22.03) deficiency [62]. With regard to the severe acquired thrombophilia due to the presence of antiphospholipid antibodies, data on the association with CVST are lacking and only case reports or small case series are available [30,63–65]. A study of 163 patients with CVST and 163 with deep vein thrombosis showed a stronger association of anticardiolipin antibodies with the former rather than the latter (17% vs. 4%) [65]. Data are scanty for other thrombophilia markers such as high FVIII and hyperhomocysteinemia. Only one case–control study investigated the association between high FVIII and CVST, showing higher levels in patients than controls [66]. Hyperhomocysteinemia is associated with a 3-fold increased risk of CVST [62,64]; however, the homozygous MTHFR C677T polymorphism, a genetic determinant of homocysteine levels, does not independently increase the risk of CVST [64,67].

Cancer

Approximately 7% of patients with CVST have a concomitant solid (cerebral or non-cerebral) or hematological cancer [16,47]. In a recent case–control study, among 594 patients with CVST the prevalence of cancer was 8.9%, for a nearly 5-fold increased risk (OR, 4.86; 95% CI, 3.46–6.81) [33]. Moreover, CVST can be a complication of chemotherapy with L-asparaginase. Out of 706 treated patients, 22 (3.1%) developed CVST, 20 of whom during treatment with L-asparaginase [68]. Although the incidence rate of CVST in patients with myeloproliferative neoplasms (MPN) is around 1%, approximately 4% of patients with CVST have an overt myeloproliferative neoplasm [69–71]. Hence, such diseases must be suspected and appropriately searched for in patients with CVST.

Systemic diseases and infections

CVST occurs in 0.5–7.5% of patients with chronic inflammatory bowel diseases, as a complication of the hypercoagulable state due to mucosal inflammation that leads to upregulation of tissue factor, high platelet count and impaired fibrinolysis [72,73]. Additional systemic conditions are vasculitis, especially Behçet disease, with an incidence rate for CVST of 3 per 1000 p-y [74], whereas few data are available on systemic lupus erythematosus and nephrotic syndrome [75]. A local infection becomes a strong risk factor for CVST through endothelial injury and activation of procoagulant pathways. The most common are otitis, mastoiditis, sinusitis, meningitis, skin or dental infections. However, in the antibiotic era the prevalence of infection-related CVST has dropped to 8–12%, although it remains higher in less developed countries [9,16,47].

Other risk factors

Additional mechanical risk factors for CVST include neurosurgery, internal jugular catheterization and lumbar puncture [3,4]. Regarding genetic causes, several loci on chromosome 6 (within the human histocompatibility complex) and chromosome 9 (close to the ABO gene) have been involved in the development of CVST [76], although these associations remain to be confirmed in large genome-wide association studies [77]. The association of CVST with other candidate genes, such as plasminogen activator inhibitor-1 4G/5G polymorphism [78] and protein Z G79A polymorphism [79], remains controversial. Janus Kinase-2 (JAK2) V617F somatic mutation, a primary molecular marker of Philadelphia-negative MPN, is also present in a small percentage (0–6.2%) of CVST without an overt MPN and it could be linked to an increased risk of cerebral thrombosis [80,81].

Risk factors in children and neonates

As in adults, CVST in children and neonates has a multifactorial etiology. Compared with adults, children develop idiopathic events less frequently and have a partially different set of risk factors due to anatomical and rheological characteristics of the cerebral circulation. The hemostatic system in children is in a dynamic state, with quantitative and qualitative differences in coagulation factors compared with adults. In neonates the hemostatic system is accelerated as a result of decreased levels of the natural anticoagulant proteins (antithrombin, protein C and protein S) that rise up to physiological adult levels at approximately 6 months after birth [82,83]. Despite this, neonates have a good hemostatic balance that can be altered by concomitant comorbidities such as systemic or local infections, dehydration, chronic renal failure and brain tumors [84,85]. In neonates there are also obstetrical predisposing conditions, including premature rupture of membranes, infections, gestational diabetes, hypertension and hypoxic ischemic injury [86]. Specifically, the compression of the skull bones during delivery can result in damage of the dural venous sinuses and this, together with typical neonatal dehydration, can increase the risk of CVST development [24,87]. Additionally, the usual supine position assumed by neonates has a major influence on intracranial venous outflow, contributing to local venous stasis. This happens particularly in the thrombosis of the superior sagittal sinus (OR, 2.5; 95% CI, 1.07–5.67) [84]. In children and adolescents, head and neck infections (otitis media, mastoiditis and sinusitis) are the most common risk factors for CVST [11,13,85,88]. Other risk factors observed in more than 50% of cases include underlying chronic diseases such as nephrotic syndrome (which confers an acquired prothrombotic state due to urinary loss of anticoagulant proteins) [89], liver diseases [11], systemic lupus erythematosus [90], malignancy

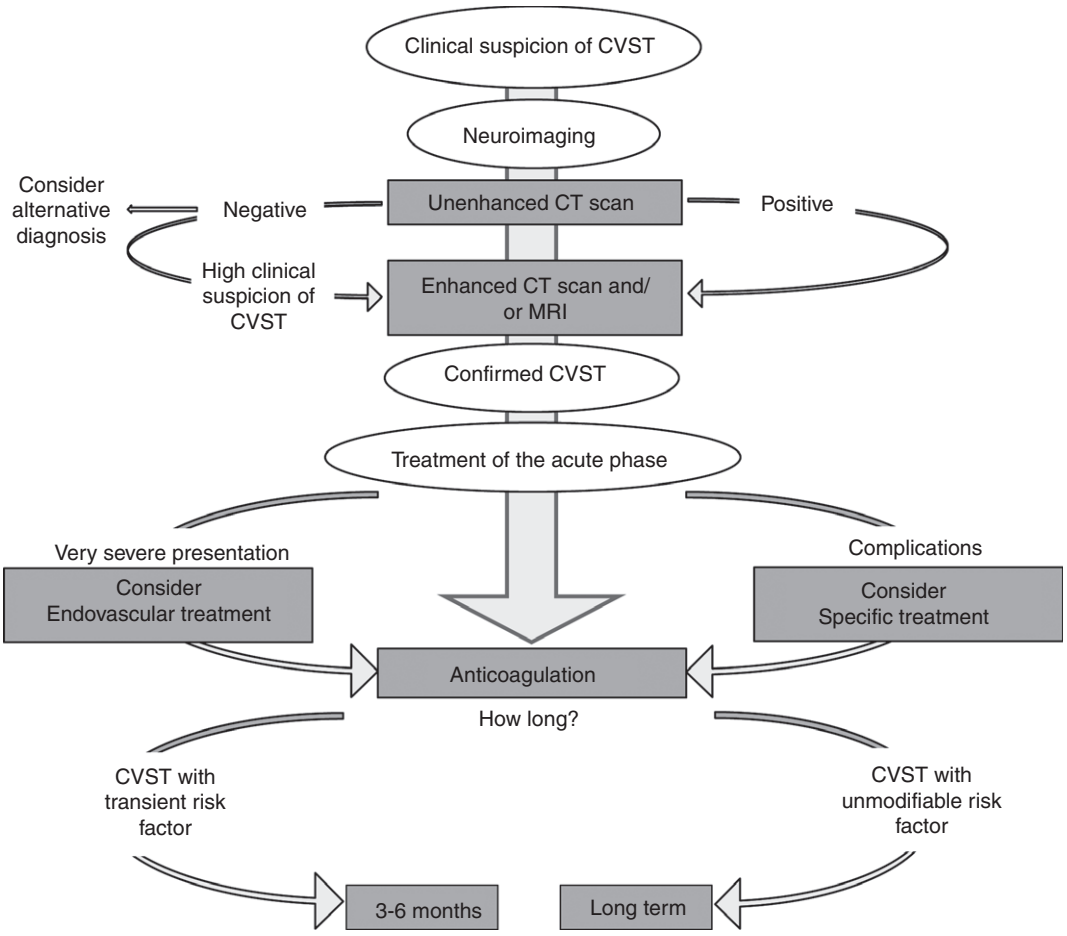

Fig. 4. Diagnostic and therapeutic algorithm in cerebral venous sinus thrombosis.

[15,91], head trauma or neurosurgery [48,49]. CVST has also been reported in children with iron deficiency anemia and to a lesser extent with hemolytic anemia, β-thalassemia and sickle cell disease[15]. Inherited thrombophilia has been poorly investigated in pediatric CVST and reported in 20% to 62% of cases [11,12,15,48]. The association of CVST with FV Leiden and prothrombin G20210A polymorphism appears weaker in children than in adults [12,15,92]. The combination of acquired thrombophilia and underlying conditions provides a major contribution to the pathogenesis of pediatric CVST [12,89].

Treatment of the acute phase

Anticoagulant treatment

The use of heparin was first described in 1942 by a British gynecologist who successfully treated a puerpera with CVST [93]. The initial indication of anticoagulation in patients with CVST comes from two small randomized controlled trials performed in the 1990s that compared heparin with placebo. The first included 20 patients and was prematurely stopped because of safety concerns due to 3/10 intracranial hemorrhages in the placebo group compared to 0/10 in the unfractionated heparin (UFH) arm [94]. The second study included 59 patients and showed a better outcome in the low-molecular-weight heparin (LMWH) arm (death or dependence rate 13% vs. 21%) [95]. A subsequent meta-analysis of the two trials showed a 13% reduction in the risk of death or dependency in patients treated with heparin [96]. None of the 18 patients with intracranial hemorrhage included in the two studies cited above and treated with heparin had worsened bleeding [94,95].An observational study including 102 CVST patients with hemorrhagic venous infarction or subarachnoid hemorrhage treated with LMWH or UFH showed a deterioration in clinical course only in 11% of patients, without a difference between the two treatment group [97]. Based on these data, current guidelines state that intracranial hemorrhage does not represent a contraindication to anticoagulant therapy in the acute phase of CVST [28]. Our personal opinion is to use subtherapeutic doses (i.e. 50–75% of the full dose) of LMWH in the case of vast intracranial hemorrhage. No consensus exists on the superiority of one type of heparin over the other. The first indirect comparison between LMWH and UFH in patients with CVST was made in the framework of the ISCVT study and showed a lower

Table 2 Ongoing clinical trials in patients with cerebral venous sinus thrombosis.

Title	NCT number	Study type and design	Interventions	Primary outcome	Estimated completion date	Age of patients enrolled
A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis (RE-SPECT CVT)	NCT02913326	Interventional randomized (phase 3)	Dabigatran etexilate vs. warfarin for 6 months	Composite rate of major bleeding and venous thromboembolism	June 2018	18–78 years
The Efficacy and Safety of Dabigatran Etexilate for the Treatment of Cerebral Venous Thrombosis	NCT03217448	Interventional randomized (phase 3)	Dabigatran etexilate vs. warfarin for 6 months	Incidence of recanalyzed veins after 6 months	January 2019	18–80 years
Comparison of the Efficacy of Rivroxaban to Coumadin (Warfarin) in Cerebral Venous Thrombosis	NCT03191305	Non-randomized, parallel assignment	Rivaroxaban vs. warfarin	Recurrent CVT or any hemorrhage	September 2018	13–50 years
Study of Rivaroxaban for CeREbral Venous Thrombosis (SECRET)	NCT03178864	Prospective randomized controlled (phase 2)	Rivaroxaban vs. standard of care	Composite rate of all-cause mortality, symptomatic intracranial bleeding, major extracranial bleeding	June 2020	≥18 years
Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT)	NCT01204333	Interventional randomized (phase 3)	Endovascular local thrombolysis vs. heparin	Favorable clinical outcome (mRS 0-1) at 12 months	Completed	≥18 years
Thrombin Generation and Thrombus Degradation in Cerebral Venous Thrombosis: Clinical and Radiological Correlations	NCT02013635	Observational prospective case-only	Non-interventional	Evolution of thrombin generation parameters and D-dimer levels from baseline and correlation with clinical presentation	Completed	≥16 years
The Role of Factor XIII Activation Peptide and D-dimer Values for the Diagnosis of Cerebral Venous Thrombosis (CVT)	NCT00924859	Observational prospective case-only	Non-interventional	To assess the overall accuracy of D-dimer and FXIII-AP (activation peptide) using a newly developed ELISA test, to exclude CVT in patients with clinical suspicion of CVT	Completed	18–85 years

incidence of disability at 6 months in the LMWH group, without differences in overall survival [98]. Subsequently, two randomized controlled trials compared LMWH and UFH. The first showed a significantly lower mortality rate in the LMWH group (0% vs. 18.8%) [99], whereas the second showed no differences between the two groups in mortality (3.8% vs. 5.6%) and in new symptomatic intracranial hemorrhage (none in both groups) [100]. UFH, with its shorter half-life and easier reversibility, can be preferred in unstable patients or in those requiring invasive procedures.

Thrombolysis and endovascular treatment

No randomized clinical trials have assessed the role of systemic thrombolysis in CVST. The most recent systematic review on this issue included only case reports and case series for a total of 26 patients [101]. Urokinase was the most frequently administered thrombolytic agent (73.1%), whereas streptokinase and recombinant tissue plasminogen activator (rt-PA) were used in 7.7% of cases each. Extracranial hemorrhage occurred in five patients (19.2%) and intracranial in three (11.5%), with two deaths. Partial or complete recanalization occurred in 16 patients (61.5%). Only case reports and small case series are available in the literature on endovascular treatment of CVST with local thrombolysis (urokinase, streptokinase or rt-PA) and mechanical thrombectomy. This treatment should be reserved for patients with a very severe presentation or rapidly declining neurological symptoms despite appropriate anticoagulant therapy, after exclusion of other causes of deterioration. Endovascular treatment is associated with a high risk of intracranial hemorrhage (7.6%) and mortality (9.2%), half of which are due to new onset or worsening of pre-existing intracranial hemorrhage [102]. These estimates are likely to be underestimated because of the publication bias in favor of successful case reports. The randomized controlled trial TO-ACT (NCT01204333) comparing local thrombolysis and heparin treatment has been prematurely interrupted after the inclusion of 67 patients because of no difference in primary outcome (mRS 0–1 at 12 months) [103].

Hence, currently available data raise concerns about safety of thrombolysis and endovascular treatment in patients with CVST.

Treatment of complications

The most severe patients present complications in the acute phase that require specific management. In the case of seizures, antiepileptic drugs are indicated to prevent recurrences, although the optimal duration of this therapy and its use as primary prophylaxis are not well established. In the case of hydrocephalus associated with neurological deterioration, shunting procedures to drain excess cerebrospinal fluid are required after temporary withdrawal of anticoagulation. Intracranial hypertension does not usually require treatment, but in symptomatic cases shunting procedures or serial lumbar puncture are required to promptly reduce intracranial pressure in case of papilledema and reduced visual acuity. Acetazolamide can also be administered to reduce cerebrospinal fluid production [28]. Rarely, patients with CVST present transtentorial herniation in the acute phase and need decompressive surgery, a lifesaving procedure. A prospective evaluation of the outcome of patients with CVST undergoing decompressive surgery is ongoing (DECOMPRESS-2 registry) and the interim analysis on 22 patients showed a 6-month mortality rate of 23.8% in patients treated vs. 100% in those not treated [104]. The role of steroids in reducing vasogenic edema is controversial; their use is not suggested in acute CVST, particularly in patients without parenchymal lesions, whereas it is recommended in CVST with an associated inflammatory disease (e.g. Behçet's disease) [28].

Treatment of the chronic phase

The optimal duration of anticoagulant therapy for secondary prevention of CVST should be decided for the single patient, evaluating the risk–benefit ratio. The absolute risk of recurrent thrombosis is low and long-term anticoagulation is reserved for patients with persistent and unmodifiable risk factors (e.g. severe thrombophilia, or solid or hematological neoplasms) and those with recurrent CVST. Whether also patients with unprovoked CVST should continue anticoagulation is not known (Fig. 4). AHA/ASA guidelines recommend that patients with CVST secondary to a transient risk factor receive anticoagulant therapy with a vitamin K antagonist (VKAs) for 3–6 months, maintaining an INR range between 2 and 3, whereas those with unprovoked CVST receive therapy for 6–12 months [24]. An exception is CVST during pregnancy, which requires therapeutic doses of LMWH possibly adjusted for bodyweight to ensure efficacy until delivery [28] because of the teratogenic effect of VKAs. AHA/ASA guidelines recommend antiplatelet therapy after a period of anticoagulation in patients with CVST without a recognized thrombophilia, although in the absence of controlled trials or observational studies this indication sounds arbitrary [105]. In line with studies conducted in patients with venous thromboembolism, we might accept the recommendation for patients with unprovoked events. Randomized clinical trials are required and the ongoing EXCOA-CVT study comparing a short (3–6 months) with a long (12 months) duration of oral anticoagulant therapy in patients with CVST will provide new insights into this crucial issue [106]. Recanalization of CVST can be considered among the criteria, potentially helping the decision on the optimal duration of anticoagulant therapy. Repeat imaging (CT or MRI) is recommended at 3–6 months from the index event or in the case of persistent or recurrent symptoms suggestive of CVST during anticoagulation therapy [24]. In the case of complete recanalization further neuroimaging is not required, whereas in the case of partial recanalization we suggest considering the possibility of prolonging anticoagulation until a reassessment at 12 months from the event. Another emerging issue in the treatment of CVST is the role of direct oral anticoagulants (DOACs), which showed a similar efficacy and a better safety profile compared with VKAs in patients with proximal deep vein thrombosis of the lower limbs or pulmonary embolism. All phase III clinical trials on the use of DOACs excluded patients with CVST and we thus have no certainties on their appropriateness for these patients, although three case series including respectively two, six and seven patients treated with rivaroxaban, confirmed its safety [107–109]. Clinical trials comparing efficacy and safety of dabigatran etexilate or rivaroxaban with warfarin or standard of care are ongoing (Table 2).

Secondary prevention

Concerning antithrombotic prophylaxis in high-risk situations after a first episode of CVST, it has been proposed to follow suggestions reported in guidelines on extracranial venous thrombosis. Concerning pregnancy, prophylactic doses of LMWH for women who discontinued oral anticoagulation are recommended [24].

Treatment in children and neonates

In children, the correction of concomitant conditions such as dehydration or infections is of crucial importance, even more so than in adults. When CVST is secondary to otitis media complicated by mastoiditis, antibiotic treatment with cephalosporins is indicated. Antibiotics are also used in patients with infection-related jugular vein thrombosis (Lemierre's syndrome), in particular against anaerobic microorganisms such as *Fusobacterium necrophorum*. In the absence of randomized controlled trials on anticoagulant treatment in children with CVST, current guidelines recommend doses of therapeutic heparin independently of concomitant intracranial hemorrhage and endovascular

treatment for patients with rapidly deteriorating neurological functions despite adequate anticoagulation, similarly to adults [110]. For neonates there is no consensus on the management of the acute phase, and both anticoagulation or a conservative approach should be considered, treating concomitant illnesses. A promising alternative to the parenteral heparin or VKAs that require laboratory monitoring (very uncomfortable in the pediatric population) are DOACs, at present under investigation in any phase trials [111]. The optimal duration of anticoagulant treatment is not well established; however, 6 weeks to 3 months are recommended for neonates, and 3 to 6 months for children [112].

Thrombolysis should be used only in highly selected patients because of the risk of bleeding, which is particularly high in neonates due to their immature hemostatic system. Moreover, the naturally low levels of plasminogen in neonates may decrease the efficacy of chemical thrombolysis and some authors suggest infusion of plasminogen through fresh frozen plasma before the procedure [110].

Conclusions

Despite its low incidence rate, CVST represents one of the leading causes of stroke in young adults. A prompt diagnosis is necessary to avoid acute complications and long-term disabilities. The mainstay of therapy is anticoagulation, even if the optimal duration of treatment is currently under investigation. DOACs represent a fascinating option for treatment of CVST, taking into consideration their safety profile and the lack of laboratory monitoring. Clinical trials with DOACs are currently ongoing in adults and children and their results will help in decision making.

Addendum

M. Capecchi and M. Abbattista reviewed the literature and wrote the paper. I. Martinelli established the structure of the manuscript and reviewed the final version. All authors approved the final manuscript.

Acknowledgements

We thank C. M. Lensing for drawing Figure 1 and A. Paolucci for the images in Figures 2 and 3.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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