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Cerebral Vein and Dural Sinus Thrombosis

Dragoș Cătălin Jianu, Silviana Nina Jianu,
Georgiana Munteanu, Flavius Traian Dan and
Claudia Bârsan

Additional information is available at the end of the chapter

Abstract

Cerebral venous thrombosis (CVT) is an uncommon disorder in the general population. At least 1 risk factor can be identified in 85% of patients with CVT. Because of the high frequency of thrombophilia among patients with CVT, screening for hypercoagulable conditions should be performed. Two pathophysiological mechanisms contribute to their highly variable clinical presentation. Four major syndromes have been described: isolated intracranial hypertension, focal neurological abnormalities, seizures, and encephalopathy. Cavernous sinus thrombosis represents the single CVT which produces a characteristic clinical syndrome. Head Computed Tomography is the most frequently performed imaging study, but Magnetic Resonance Imaging of the head combined with Magnetic Resonance venography are the most sensitive studies. Acute phase therapy for CVT focuses on anticoagulation, management of seizures, increased intracranial pressure, and prevention of cerebral herniation. The majority of patients have a complete or partial recovery, however they have an increased incidence of venous thromboembolism. Clinical and imaging follow-ups 3–6 months after diagnosis are recommended to assess for recanalization.

Keywords: cerebral venous thrombosis, thrombophilia, isolated intracranial hypertension, magnetic resonance imaging of the head, magnetic resonance venography, anticoagulation

1. Introduction

Rare (0.5–1% of all strokes), but alarming disease, cerebral venous thrombosis (CVT) has a higher frequency among young adults (<40 years of age), patients with thrombophilia, and women who are pregnant or using oral contraceptives [1–4]. The most frequent symptoms are headache,

papilledema, seizures, motor, sensory or language deficits, altered mental status and decreased consciousness. CVT can be caused by multiple predisposing conditions and precipitants. At least one risk factor can be identified in more than 85% cases, multiple risk factors, in about ½ of patients, while in less than 15% no underlying cause can be found [1, 2, 5]. Contemporary brain imaging techniques [angiography, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA)] allow the diagnosis of benign forms of CVT with minimal, nonspecific symptoms and spontaneous recovery [1, 3]. The CVT treatment is based on a combination of etiologic and symptomatic medications. Currently, the main treatment of choice for CVT is heparin (intravenous heparin or subcutaneous low-molecular-weight heparin) in therapeutic dosages [1, 5]. The CVT prognosis depends on the early detection, but it should be mentioned that mortality trends have diminished over the last decades [6]. Because of its frequently misleading presentation, its wide spectrum of causes, its unpredictable course, and its occasional treatment problems, CVT remains a challenge for the clinician [1, 6]. We also want to emphasize that, due to its features, CVT should remain a disease of interest not only for neurologists, but also for other specialists – neurosurgeons, ear, nose and throat (ENT) specialists, ophthalmologists, hematologists, obstetricians, internists, and oncologists [5].

2. Dural sinuses and encephalic veins anatomy

2.1. Encephalic veins

The veins within the cranium contain approximately 70% of the cerebral blood volume (**Figure 1**) [7]. Blood of the brain is drained by the cerebral venous system which consists of the cerebral veins and dural venous sinuses. The cerebral veins don't follow the same path as the arteries. Emerging as fine branches from the substances of the brain, the cerebral venous blood vessels form a pial plexus from which arise the larger venous channels (cerebral veins) which empty into the sinuses of the dura mater. Cerebral veins have thin walls and no valves; they are linked by multiple anastomoses, which allows the development of a collateral circulation and the reversal of blood flow toward the head and brain if there is an occlusion [1, 5, 8, 9].

Cerebral veins comprise three groups: (a) *the superficial venous system*, (b) *deep venous system*, and (c) *posterior fossa veins*: [5].

a. Due to its high proportion of number, course, and anastomoses, *the superficial cerebral (cortical) venous system* is difficult to diagnose in cases of occlusion. The superficial veins are divided into superior, middle (sylvian), and inferior cerebral groups. They drain the major part of the cerebral cortex. The superficial cerebral veins are linked by Trolard's great anastomotic vein, which connects the superior sagittal sinus (SSS) to the middle cerebral veins, which are themselves connected to lateral sinus (LS) by Labbé's vein. The frontal, parietal and occipital superior cerebral veins drain into the SSS. The middle cerebral veins consist of a superficial and a deep vein. The superficial middle vein empty into the cavernous sinus, while the deep one, drain into the basal veins of Rosenthal [1, 5–7, 9].

b. Deep white matter, the corpus callosum, the basal ganglia, and the upper brainstem are drained *by internal cerebral and basal (Rosenthal) veins* which join to form *the great vein of*

Galen and empty, together with the inferior sagittal sinus (ISS), into the straight sinus (SS). In contrast to the superficial veins, the deep system is consistent and is always visualized at angiography, thus any thrombosis in this system is easily recognized [1, 3, 5, 6].

The two cerebral venous systems are connected through many anastomoses [6].

c. *Veins of the posterior fossa* may be divided into three groups: superior veins (draining into the galenic system), anterior veins (draining into the petrosal sinuses), and posterior veins (draining into the troncular and neighboring SS and LS). They are variable in course, and number making the angiographic diagnosis of their occlusion, extremely difficult [1, 5].

2.2. Dural sinuses

The dural sinuses represent a system of intercommunicating trabeculated endothelium-lined channels located between the meningeal and periostal layers of the dura (**Figure 1**). The walls of the sinuses are formed by the inner and outer fibrous layers of the dura mater. Inside of dural sinuses are found the Pacchioni's or arachnoid granulations, which play an essential role in the cerebrospinal fluid (CSF) resorption, especially in SSS and SL [6, 9].

The major dural sinuses are: SSS, ISS, LS, cavernous sinus and SS; they empty into the two internal jugular veins (IJV) to drain into the superior vena cava. Dural sinuses are divided into posterior-superior (P-S) and antero-inferior groups (A-I). P-S comprises the SSS, ISS, LS, SS, and occipital sinus. The A-I group includes the superior and inferior petrosal sinuses and the cavernous sinus. The confluence of the sinuses (torcular herophili) is formed by the junction of SSS, straight, occipital and transverse sinuses [1, 5–7].
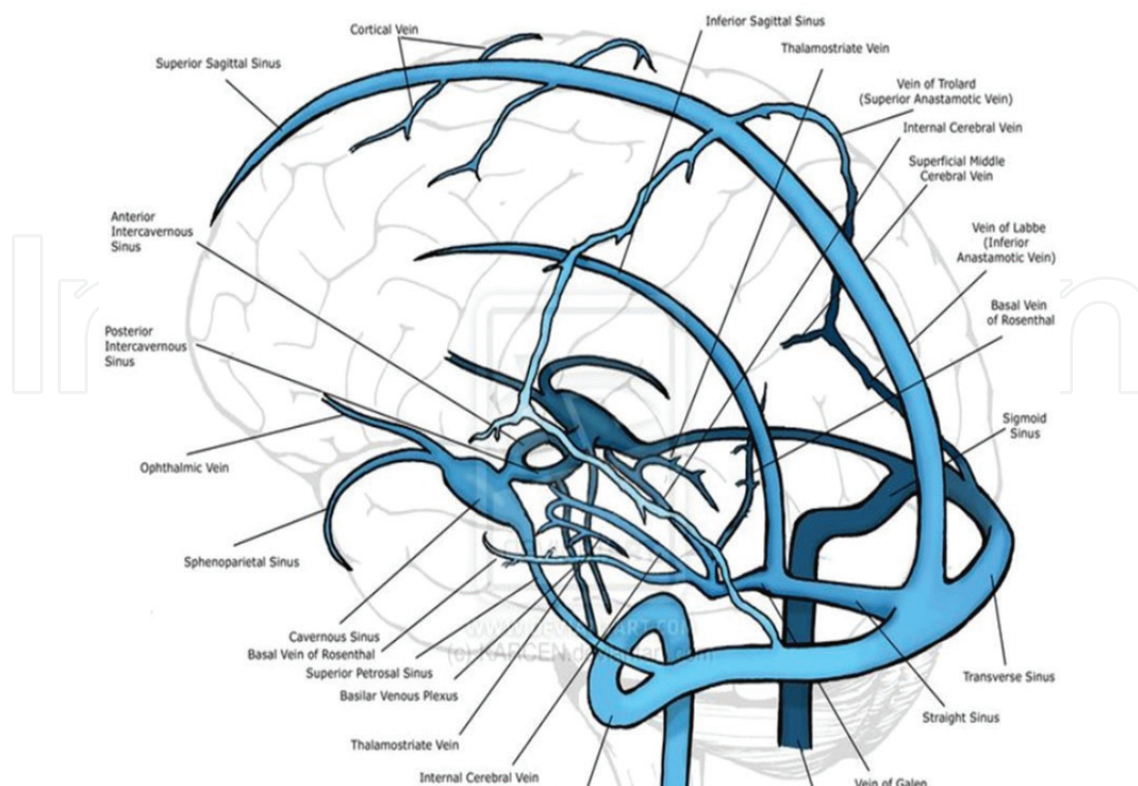
Figure 1. Dural sinuses and encephalic veins anatomy [70].

The superior sagittal sinus (SSS) is located in the attached margin of falx cerebri, receives superficial cerebral veins and drains the major part of the cerebral hemispheres. It also receives the diploe, dura mater, the scalp, and the pericranial veins which explains some cases of SSS thrombosis after cutaneous infections or head trauma. The SSS along with LS sinuses play an important role in CSF circulation, considering that CSF pressure depends directly on the intracranial venous pressure [1, 6, 7, 9].

Each lateral sinus (LS) consists of two sections: the transverse portion and the sigmoid portion which drain blood from cerebellum, brainstem, and posterior portions of the cerebral hemispheres. They also receive some of the diploic veins and some small veins from the middle ear thus becoming vulnerable to infections thrombosis in patients with mastoiditis or otitis media. Asymmetry of the LS is frequent (50–80% of the cases) [1, 3, 6]. The right LS which is often a direct continuation of the SSS, is usually larger than the left so an isolated lack of filling of the left transverse sinus is thus suggestive more of hypoplasia than of thrombosis [1, 7].

Cavernous sinuses are complex, multiseptated extradural venous spaces located on each side of the sella turcica. They drain the blood from the orbits and from the anterior part of the base of the brain receiving superficial cortical veins, the ophthalmic (superior and inferior) and facial veins. Each cavernous sinus has important anatomical relations with other structures. Thus, the oculomotor and trochlear-cranial nerves, along with the ophthalmic and maxillary branches of the trigeminal nerves, traverse along the lateral wall of the cavernous sinuses, whereas the abducens nerve and the cavernous portion of the internal carotid artery (ICA) lie within the sinus itself. Infection is still the leading cause of cavernous sinuses thrombosis as a consequence to infections of the face or sphenoid sinusitis. The cavernous sinuses communicate with each other via *intercavernous sinuses and basilar venous plexus*, and drain into the *petrosal sinuses (superior and inferior)* which empty into the sigmoid sinuses and the IJVs [1, 3, 6, 7].

The inferior sagittal sinus (ISS) receives blood from the corpus callosum and the cerebellum (through the deep cerebral veins) and it becomes continuous with SS [9].

The straight sinus (SS) is formed by the junction of ISS with the vein of Galen. It has a triangular lumen and is situated at the junction of the tentorium cerebelli with the falx cerebri. SS runs postero-inferiorly and ultimately joins torcular Herophili at the internal occipital protuberance [9].

The occipital sinus is the smallest dural venous sinus, receiving tributaries from the margins of the foramen magnum. It runs along the inner surface of the occipital bone and may anastomosis with the sigmoid sinuses and *posterior internal vertebral plexus* that drain into the torcular Herophili [10].

The internal jugular veins (IJV) are the continuation of the sigmoid sinus. They drain blood from the brain and the superficial parts of the face and neck. In contrast to the cerebral veins, they have valves in order to prevent blood going upwards in cases of increased intra-thoracic pressure [9].

The major cerebral venous outflow pathways are represented in adults by the IJV, for supine position, and the vertebral venous system for the upright position [11].

3. Epidemiology

The prevalence of CVT is higher than previously reported probably because this rare type of stroke is now more frequently diagnosed due to an increased awareness and improved imaging techniques [12, 13]. CVT represent 0.5–1% of all strokes and may affect all age groups – from neonate to the very old [14]. CVT is more common in children than in adults, and among children, is more frequently diagnosed in neonates than in older children. The peak incidence in adults is in their third decade: the median age in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort was 37 years, with only 8% of the patients older than 65 [5, 15–16]. CVT has a prominent differential sex prevalence, with a female-to-male ratio of approximately 3:1, with an even more marked difference in the age range of 31–50 years. The female predominance of CVT has been attributed to hormonal factors considering that the incidence is sex-independent in children and in the elderly [5, 16–18].

4. Risk factors

Several disorders can cause or predispose patients to CVT and often, this condition proves to be multifactorial, meaning that the identification of a risk factor or a cause should not deter from a search for other causes, in particular inherited or acquired thrombophilia [1, 3, 16, 19]. Supporting this affirmation, the ISCVT results showed that at least one risk factor can be identified in more than 85% of patients with CVT and multiple risk factors, in about half of them. The most frequent risk factors are prothrombotic conditions, oral contraceptive (OC) use, puerperium or pregnancy states, infection and malignancy. Among the CVT risk factors, thrombophilic disorders are the most frequent; only for the cavernous sinus, the main cause of thrombosis remains the skin infections of the face [5].

In the pre-antibiotic era, *localized or systemic infections were the most common cause of dural sinus occlusions.* Septic CVT is usually caused by pyogenic infections of the mastoid air cells, the paranasal sinuses, face, ears, scalp, or throat. It may also result as a complication of meningitis, secondary to brain or epidural abscesses or after an open traumatic injury. However, since the introduction of antibiotics, septic thrombosis, has become a relatively rare, although severe condition [20].

In the 624 patients included in ISCVT, 34% had a form of *thrombophilia* and an inherited thrombophilic defect was detected in 22% of them. It is important to mention that usually an additional precipitating factor is present in patients with thrombophilia who develop CVT [4, 5, 16, 19].

Inherited thrombophilias are the main genetic disorders associated with CVT. Three highly prevalent mutations have been linked to thrombosis: factor V Leiden, factor II-the prothrombin variant (PT 20210A), and the homozygosity for MTHFR C677T. Among them, the factor V Leiden and the prothrombin gene mutation are the most frequent [3, 21–23]. The Q506 mutation in the gene coding for factor V (factor V Leiden) causes inherited resistance to activated protein C. Factor

V Leiden is the most prevalent inherited coagulation disorder and an important cause of CVT, being associated with a 9-fold higher risk, especially if females with this mutation take OC or become pregnant [12, 14, 20]. The prothrombin G20210A mutation (PT20210A) is considered the most important genetic thrombophilic risk factor associated with CVT. This mutation is present in about 2% of Caucasians causing an elevation of the plasmatic factor II level [14, 22]. According to Martinelli, PT20210A determines a 10-fold increase in the cerebral thrombosis risk, especially in OC users [12, 24]. Other genetic coagulation disorders reported to be involved in CVT include: plasminogen deficiency, decreased release of plasminogen activator, sickle cell disease (homozygous sickle cell anemia), and elevated levels of factor VIII [20, 22].

Acquired thrombophilias. Antiphospholipid antibodies are directed against phospholipid-binding plasma proteins and include anticardiolipin antibody and antibodies directed against β 2-glycoprotein. They were described in patients with lupus erythematosis, other connective tissue diseases and as isolated abnormalities, being strongly associated with arterial and venous thrombosis [21].

Antithrombin III and proteins C and S are natural inhibitors of coagulation. They can be deficient on a hereditary basis or be reduced by disease. Congenital deficiency of antithrombin III may be quantitative or qualitative and is usually an autosomal-dominant condition. Inherited deficiencies of proteins C and S (both vitamin K dependent anticoagulants) can also contribute or cause hypercoagulability. Acquired deficiencies of antithrombin III may be associated with liver diseases or renal loss (nephrotic syndrome) [20].

Hyperhomocysteinemia (HHcy) is a disorder that is defined by an elevated plasma homocysteine (Hy) concentrations. HHcy may have a toxic effect on the vascular endothelium affecting the clotting cascade. Increased plasma Hcy levels can be caused from several different genetic mutations in enzymes involved in Hcy metabolism (hereditary forms). Within these, the mutation of the MTHFR C677 → T gene is the most prevalent. There were also described acquired forms of HHcy which are determinated by low levels of folic acid, vitamin B6 or vitamin B12. HHcy is known to be associated with an increased risk for deep venous thrombosis (DVT) and arterial occlusive disease [12, 14, 19]. According to different studies, HHcy could be considered an independent and strong risk factor for CVT [19, 25, 26].

The gender-specific risk factors – pregnancy, postpartum state, oral contraceptive (OC) use and the hormone replacement therapy – are the most frequent risk factors in women with CVT, they being responsible for the marked feminine preference of this condition [4, 6, 18].

Pregnancy and puerperium In high-income countries, 5–20% of all CVT are related to pregnancy or puerperium, according to ISCVT, the peripartum etiologies being responsible for 15% of CVT cases [16, 27–29] However, the incidence is much higher in low-income countries where puerperium is the most common risk factor for CVT accounting for 31% of cases [27, 30, 31]. Explanations for the frequency of intracranial venous thrombosis in pregnancy and the puerperium include poverty, absence of antenatal care, home delivery, vegetarian diet, depletion of vitamin and protein stores and dehydration associated with primipara and anemia [32]. Most pregnancy-related CVT occur in the third trimester or, more frequently,

in the first 3 week post-partum. In these cases, CVT could be accompanied by venous thromboses outside the nervous system (pelvic or lower extremity phlebothrombosis and pulmonary embolism), probably, as a consequence of the hypercoagulable state and the venous stasis that occurs during pregnancy [3, 17, 20]. The prothrombotic changes induced by pregnancy include increasing of fibrinogen and several coagulation factors and decreasing of antithrombin III and plasminogen. These alterations in the coagulation system persist at least during early puerperium when the hypercoagulability worsens as a result of volume depletion, trauma and additional risk factors as infection, unhygienic environments, certain rituals, higher birth rates, instrumental delivery or cesarean section [3, 14, 28, 33, 34]. On the other hand, *pelvic phlebothrombosis may determine CVT via the venous plexuses of the vertebral canal, and the basilar venous plexus.*

Estrogens, whether administrated for contraception or therapeutic purposes (replacement therapy, suppression of lactation), are associated with a significant risk for venous and arterial thrombosis. Particularly, the administration of OC (especially the third-generation agents) is considered to be an independent risk factor for CVT, the great majority of younger no pregnant women with this condition being OC users [3–5, 14]. It is also important to mention that the risk of thrombosis, whether intra- or extracerebral in women taking OC is almost 6 times higher than that of non-users if this contraception method is combined with an underlying hereditary prothrombotic abnormality like those listed above [5, 14, 17, 35]. In most of the cases, the use of OC is found together with other conditions such as systemic lupus erythematosus, Behçet's disease or inherited thrombophilia. However, in about 10% of the CVT cases, the prothrombotic effect of OC remains the only identifiable etiologic factor [1]. Pregnancy and OC use represent transient risk factors for thrombosis and they are not necessarily associated with a higher risk for recurrence [17].

Hormonal abnormalities may also interfere with normal coagulation mechanisms in males. Supporting these statement, we mention the reported case of a young healthy man who develop extensive dural sinuses thrombosis after taking intramuscular injections of androgens for body building [20, 36].

In the ISCVT, *cancers* account for 7.4% of all CVTs [16]. Mechanisms associated with CVT in cancer patients include: direct tumor compression, tumor invasion of cerebral sinuses, leukostasis, the hypercoagulable state caused by increase in acute-phase reactants or altered coagulation factors from therapy (chemotherapeutic and hormonal agents).The most frequent cancers linked with CVT are the hematologic malignancies, breast tumors, nephroblastoma, Ewing's tumor, gallbladder carcinoma, medulloblastoma and medullary carcinoma of the thyroid [14, 20].

Hematologic disorders. Philadelphia-negative myeloproliferative disorders (MPDs), especially polycythemia vera (PV) and essential thrombocythemia, are associated with a high risk of venous thrombosis, CVT being reported as a complication of these conditions in 2.8% of the ISCVT cases. The acquired Janus kinase 2 V617F mutation (JAK2 V617F) has been found in more than 90% of patients with PV and in about 50% of those with essential thrombocythemia. The presence of JAK2 V617F is associated with an increased incidence of major thrombosis and a poor prognosis. This mutation has been also identified in patients with venous

thrombosis occurring in up to 15 years before diagnosis of overt MPD [37]. Other hematological conditions can determine or predispose to venous occlusion and among them we mention: myelofibrosis, myeloid metaplasia, gammopathies, paroxysmal nocturnal hemoglobinuria, iron deficiency anemia, heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura [14].

Vasculitides. Numerous systemic autoimmune disorders has been associated with CVT: inflammatory bowel disease, systemic lupus erythematosus (SLE), with or without nephrotic syndrome, Behçet's disease, Sjögren's syndrome, Wegener's granulomatosis, sarcoidosis, Hughes-Stovin syndrome, malignant atrophic papulosis [1, 4, 14].

Local causes such as head trauma, brain tumors, porencephaly, arachnoid cysts or arteriovenous malformations, and *mechanical factors* including cranial and systemic surgery, epidural blood patch, spontaneous intracranial hypotension, jugular venous cannulation and lumbar puncture can also determine dural sinus and cerebral venous occlusions [1, 4, 14, 20].

Other conditions have been associated with CVT in case reports or small series including severe dehydration (mostly in children and elderly), malnutrition, cardiac failure, and chronic obstructive pulmonary disease [5, 16, 20].

There is still a significant number of *idiopathic CVT* cases. According to ISCVT results, in almost 13% of adult CVT patients extensive search reveals no underlying cause. We also want to emphasize that among these patients, in 37% of those over 65 years no risk factors could be identified [16].

5. Pathophysiology

The venous system of the brain is a complex three-dimensional structure that is often asymmetric, having a significantly more variable pattern than the arterial anatomy (**Figure 2**). The cerebral vasculature plays a major role in maintaining the local physiological hemodynamic course in order to meet the metabolic needs of the brain. Based on principles of physics applied to intracranial contents, within the closed skull, the sum of brain volume plus cerebral spine flow (CSF), plus cerebral blood volume always remains constant and, consequently, an increase in one of these parameters should cause a reduction in one or both of the remaining two. Therefore, the permeability of the vascular bed is essential in order to preserve the cerebral compliance [38, 39].

The cerebral blood drainage depends on the gradient between venous pressure and intracranial pressure. Also for tissue perfusion to occur, the blood pressure in the feeding artery must exceed the pressure in the tissue and draining veins. Another pressure difference, the one between CSF and SSS, maintains the CSF absorption across the arachnoid villi into the SSS [6, 20, 39].

CVT is a multistep process that usually begins when thrombus partially occludes a dural sinus. In situ thrombus formation occurs due to the usual pathogenic factors – activation of the coagulation system and blood hypercoagulability [1, 3, 20]. The vessel wall is usually normal. The thrombosis may progresses, obstructing first the sinus and then the smaller
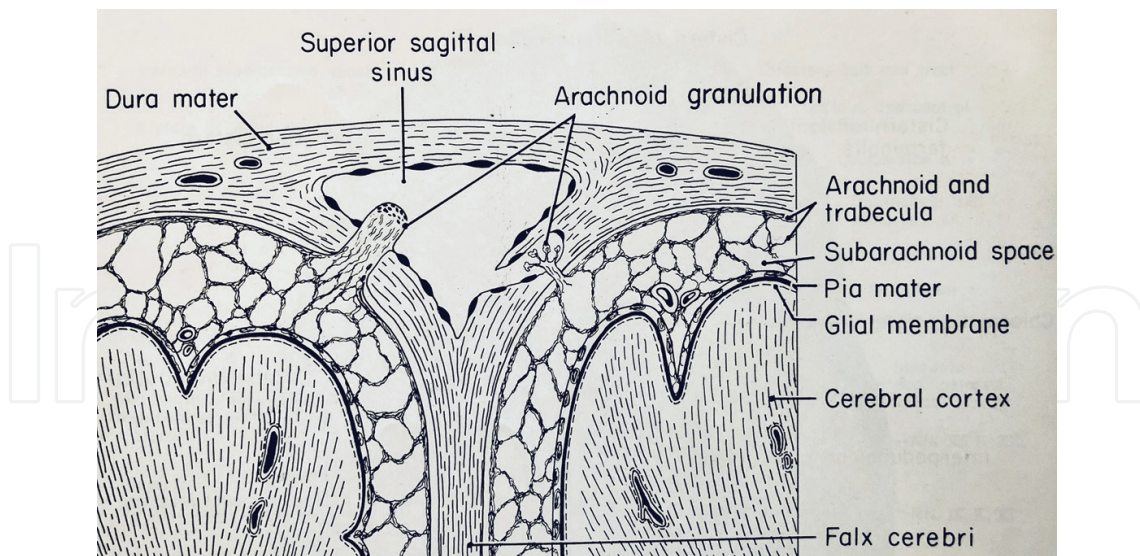
Figure 2. Diagram of meningeal-cortical relationships [8].

venous tributaries. The distribution of the possible consecutive lesions depends on a variable balance between prothrombotic and thrombolytic processes and compensation of occlusions by collateral circulation. Symptoms usually appear when this compensatory mechanism is no longer effective [3, 9, 39].

The two major pathophysiological mechanisms responsible for the clinical manifestations of CVT are: (1) *increasing of venular and capillary pressure,* and (2) *decreasing of CSF absorption* [4].

1. Thrombosis of cerebral veins or sinuses causes a progressive increase of venular and capillary pressure.

   In the early stages of venous obstruction, the extensive collateral circulation within the cerebral venous system provides a significant degree of compensation. Therefore, an adequate perfusion of the affected brain tissue might still be possible at lower flow rates, if the blood is effectively drained through collateral pathways and the pathological pressure changes are thus, neutralized. As a result, large areas of the brain can be functionally and metabolically impaired, but not irreversibly damaged [6, 39].

   However, prolonged intravenous hypertension corroborated with a poor collateral flow will result in extension of the thrombosis within cortical venous tributaries, lowering even more the cerebral perfusion pressure [39], which will lead to:

   a. local ischemic injury and cytotoxic edema,

   b. disruption of the blood–brain barrier leading to vasogenic edema, and.

   c. venous and capillary rupture culminating in parenchymal hemorrhage and, less frequent, subarachnoid hemorrhages [4].

   In milder cases, dural sinuses thrombosis may cause only an increase in intracranial venous or CSF pressure with minimal symptoms like headache or papilledema, or can remain

completely latent. Usually, the occlusion of cerebral veins is the one that leads to so-called venous infarct. The most common anatomic presentation is that of extensive bilateral hemorrhagic infarcts, located in the superior and internal parts of both hemispheres, due to thrombosis of the SSS and its tributary cortical veins [1, 6]. The limited drainage that occurs due to CVT and resulting increased venous pressure, often causes fluid to back up into the brain, causing vasogenic edema. This type of edema accumulates within the extracellular space of the cerebral and cerebellar white matter under the influence of hydrostatic pressure (increased blood pressure and blood flow) and osmotic gradients. Vasogenic edema does not necessarily imply neuronal injury, considering that the fluid in the extracellular compartment can potentially be removed. On the other hand, cytotoxic edema is caused by energy failure with movement of ions and water across the cell membranes into cells. The intracellular edema, as a consequence of ischemia, is associated with the presence of a large volume of dead or dying brain cells and implies a bad outcome [20]. In venous infarcts, the vasogenic edema is much more prominent that the cytotoxic type as has been also proven by diffusion-weighted imaging which sustains the fact that the venous infarcts are different from arterial ones and explains, at least partly, the much better recovery reported in those with CVT [1, 19]. Brain edema and increased intracranial pressure cause headache, decreased consciousness and vomiting, but the most important concerns related to these pathological processes are the pressure shifts and the risk for brain herniation which can be life-threatening due to possible pressure-related damage to adjacent tissues [20]. The raised venous and capillary pressure also determines the occurrence of vessel damages and erythrocytes diapedesis through the blood–brain barrier disruptions, both resulting in brain hemorrhage. However, the neuronal damage associated with CVT-induced hemorrhage is often less severe than the lesions caused by arterial ischemia [20, 39].

2. Cerebrospinal fluid is normally absorbed through arachnoids granulations especially into the SSS and LS. Another effect of cerebral sinuses occlusion, especially of the SSS and LS is the decreasing of CSF absorption which, ultimately raises the intracranial pressure. Consequently, increased intracranial pressure worsens venular and capillary hypertension and contributes further to parenchymal hemorrhage and edema [4, 6].

Histological analysis in CVT patients reveals dilated and congestionated veins, brain edema with flattened gyri, obliterated sulci and compressed ventricles, ischemic neuronal damage. The thrombus is like other venous thrombi (rich in red blood cells and fibrin and poor in platelets-when it is fresh; and replaced by fibrous tissue, sometimes with recanalization-when it is old) [1, 6, 9, 20].

6. Clinical presentation

CVT present with a wide spectrum of symptoms, signs and modes of onset. Usually, these conditions are characterized by a gradual or stepwise development of symptoms. Thus, in 50–80% of cases the onset is subacute (over 48 h, but under 30 days); in a third of the patients the onset is acute (under 48 h), and in 7%, chronic (over 30 days). Besides

puerperal and infectious cases which tend to present acutely, the progressive increase in symptoms and fluctuating course are the rule in patients with other causes of venous occlusion. The gradual onset of CVT' symptoms can be explain by the slow evolution and propagation of thrombosis and the potentially broad collateralization which may be able to maintain for a while an adequate drainage of cerebral blood [1, 5, 16, 20].

In patients with altered mental status associated with focal neurological deficits, seizures and headaches, CVT always must be considered a possible diagnosis. On the other hand, there were reported cases with atypical presentation and occasionally, isolated symptoms such are headache, a single seizure or nonspecific behavioral symptoms. In young children and especially neonates, CVT have a mostly nonspecific clinical presentation with seizures, respiratory distress syndrome, hypertonia, lethargy or coma [5, 9].

The clinical features of CVT depend on the following factors: gender and age of the patient, interval from onset to admission to hospital, site and number of thrombosed sinuses and veins and presence of parenchymal lesions [5, 9, 19].

The most common syndromes of CVT are: isolated intracranial hypertension, focal neurological deficits, seizures, and subacute encephalopathy. Depending on the extent and location of cerebral venous occlusion, these syndromes may be found in combination or as isolated groups of symptoms.

1. *Isolated intracranial hypertension* is the most homogeneous clinical pattern found in CVT (40%). It is characterized by headache with or without vomiting, papilledema and sixth nerve palsy [1, 4, 5, 20].

   Headache is an extremely common symptom in patients with CVT, being present in almost 90% of patients in the ISCVT [14–16, 20]. It is the earliest symptom in 2/3 of cases. It is also important to mention that headache is much more common in patients with venous thromboses than in patients with cerebrovascular ischemic arterial disease [6, 20]. The presence of this symptom in CVT cases can be explained by the increased intracranial pressure and the local inflammatory reaction which activates pain-sensitive fibers existing in the walls of the occluded sinuses, dura and overlying skull [14, 19, 20]. The headache associated with CVT is mostly gradual in onset, diffuse, severe in intensity, progressive and permanent; it may worsen with Valsalva maneuvers or position change [1, 9, 40]. Its features can be misleading, mimicking migraine or the typical thunderclap headache of subarachnoid hemorrhage; in puerperal cases, it can be misdiagnosed as post-dural puncture headaches. Nevertheless, it is almost every time accompanied by other neurologic signs [1, 14, 34]. However, isolated headache without focal neurological findings or papilledema occurs in up to 25% of patients with CVT, being typically associated with LS thrombosis [6, 14, 19].

   Papilledema occurs in about 25–40% of patients with CVT; it can cause transient visual impairment, and if prolonged, optic atrophy and blindness. Visual loss is usually insidious, with progressive constriction of the visual fields and relative sparing of central visual acuity. Delayed diagnosis may expose the patient to an increased risk of later visual deficit [6, 14]. Transient loss of vision can occur in association with spells of intense headache and papilledema [5].

2. *Focal neurological deficits* are inaugural in 15% of cases and are present in about half of patients with dural sinus and cerebral veins occlusions during the course of the disease [1]. Focal cerebral signs include central motor and sensory deficits, aphasia or hemianopia and are consequences of focal parenchymal abnormalities [9, 15, 20]. Unilateral or, less frequently, bilateral motor deficits are the most common focal findings and may be present in up to 40% of patients. Among this signs, hemiparesis is probably the most common. Sensory deficits are less frequent. Other possible symptoms associated with CVT are aphasia (usually in left LS thrombosis), hemianopia and ataxia (found in posterior dural sinuses occlusion) [4, 5, 20].

3. *Seizures* (focal, generalized or even status epilepticus) are the inaugural symptom of CVT in about 12–15% of cases and are present at some point during the disease in about 40% of patients with an even higher incidence in peripartum (76%) and neonates (71%). Particular attention should be paid to pre-eclamptic patients with CVT that develop seizures, considering that in these cases the diagnosis can be delayed until the empirical treatment for eclampsia fails to resolve the seizures [1, 4, 20, 34] Seizures are about equally divided between focal and generalized types, and the association of both types is common [1]. It is important to know that seizures are more frequently seen in CVT than in other stroke types [4, 5, 15]. According to numerous studies, a higher risk for inaugural and early seizures was found in patients with supratentorial parenchymal lesions (especially anterior to the central sulcus), intracranial hemorrhage, SSS and cortical veins thrombosis (which drain venous blood from the motor and sensory cortices), and in those who have motor or sensory deficits [4, 19, 41–44]. Also, the patients with presenting seizures are considered to have a higher risk of early seizures. On the other hand, the risk of early seizures in patients without supratentorial parenchymal lesions or presenting seizures was very low. Also, the antiepileptic drug (AED) prophylaxis significantly decreased the risk of early seizures in CVT patients presenting the predisposing factors listed above [41].

4. *Subacute encephalopathy*-manifested mostly as a depressed level of consciousness (varying from drowsiness to deep coma) is present in about half of cerebral venous disease cases and is found in patients which are often either very old or very young [1, 4]. Alteration of consciousness is usually a late one, but it can be found in about 15% of patients with CVT at hospital admission [1, 15]. It may occur when CVT is a terminal event during another severe condition, or as a result of extensive acute CVT with large venous infarcts and bilateral thalamic involvement, cerebral edema, or parenchymal hemorrhages that cause brain herniation. In CVT the alteration in level of consciousness is mostly reversible, however, coma at admission remains the strongest predictor of a poor outcome [20, 15]. The differential diagnosis of CVT encephalopathy includes encephalitis, disseminated intravascular coagulation and cerebral vasculitis [1]. Psychiatric disturbances (irritability, anxiety, depression, delirium) in association with CVT are relatively infrequent (6%) and may be confused to postpartum psychosis [1, 9].

The clinical pictures of CVT differ according to the location of the occluded sinus or vein, however, in approximately two thirds of patients thrombosis affects multiple veins or sinuses [1, 5, 20, 45]. The two most frequent sites of thrombosis are the SSS (62–80%) and the LS (38–86%). The isolated involvement of one sinus occurs in a minority of cases: less than 30%

for SSS and 10% for LS [1, 16, 45]. Cerebral veins are often involved but almost never in isolation. Thrombosis of the galenic system is rare. It is important to know that the management of CVT it is not influenced by the topographic diagnosis [1, 20].

Superior sagittal sinus (SSS) thrombosis is the most commonly affected and is the favorite location for thrombosis during the puerperium. The usual presentation of the isolated SSS occlusion is that of an isolated intracranial hypertension. Symptoms and signs depend on the involvement of cerebral veins and other dural sinuses, especially LSs. Extension to cortical veins is followed by the onset of a focal motor or sensory deficit (more marked in the leg), focal or generalized seizures. Bilateral motor signs may also occur as a consequence of the bi-hemispheric injuries caused by the SSS thrombosis [1, 14, 20].

Lateral sinus (LS) thrombosis has variable presentation. Patients with isolated thrombosis of LS usually present a pseudo tumor syndrome (isolated intracranial hypertension) [1, 19, 20]. The infectious etiology is much more common in LS thrombosis than in SSS occlusion. Isolated LS thrombosis has mostly been reported in otologic patients as a consequence of ear and mastoid infections, hence the term "otitic hydrocephalus" [20, 45]. The symptoms related to an underlying otic infections in patients with LS thrombosis are relatively characteristic. Fever, headache, neck pain and neck tenderness, vertigo, nausea and vomiting, diplopia caused by sixth nerve palsy and signs of fifth nerve irritation manifested as temporal and retro-orbital pain are often present. The mastoid region may be sensitive to finger percussion. Decreased alertness may occur [14, 20]. Intracranial hypertension is more common after right-sided LS thrombosis because the left LS is often hypoplasic; in these patients right LS occlusion will cause a bilateral drainage impairment, affecting structures on either side of the tentorium, especially the inferior portions of the temporal lobe and cerebellum. Therefore, combined temporal lobe and cerebellar signs on one side suggest LS thrombosis [20]. Fluent aphasia, is common in left transverse sinus thrombosis (40%) and can be accompanied by right hemianopia or superior quadrantanopia. Right temporal lobe involvement causes an agitated state and left visual field defect. Nystagmus and gait ataxia are the typical signs of cerebellar involvement [4, 5, 20]. The thrombotic process spreads, in most of the cases, to other sinuses and veins, especially to the SSS. Focal signs are present when thrombosis extends to superior or inferior petrosal sinuses (5th and 6th cranial nerves involvement), SS and deep venous system, adjacent cortical veins and the jugular bulb (9th, 10th and 11th cranial nerves involvement) [1, 5]. In rare cases, a patient with thrombosis limited to the left LS (without involvement of tributary veins), presents an atypical clinical picture (migraine-like acute isolated headache), and the thrombosis is not due to an ear infection, but to a thrombophilia [4, 46]. In consequence, we have to systematically look for LS thrombosis (and other CVT) in patients with recent headache even in the absence of associated symptoms and signs, and ear infections.

Cavernous sinus thrombosis usually has an infectious cause. The most common germs implicated in septic cavernous sinus thromboses are staphylococcus, streptococcus and pneumococcus [20, 47]. Cavernous sinus thrombosis represents the single CVT which produces a characteristic clinical syndrome which includes: chemosis, conjunctival edema, proptosis and painful complete or partial ophthalmoplegia [1, 5, 9, 20]. Papilledema is common and may be associated with hemorrhages of the retina. Symptoms generally start in one eye, but within a

couple of days the other eye is usually affected via intercavernous sinuses. Headache, facial pain and fever can precede the typical syndrome described [9, 20]. The direct relationship between the cavernous sinus and the dura results in symptoms of meningeal irritation. When the occlusion extends to other sinuses and cortical veins, seizures and motor weakness may occur [9, 47]. Head trauma, surgery on intracranial or facial structures, prothrombotic states and thrombosis of dural arteriovenous fistulas can result in aseptic cavernous sinus thrombosis. The signs and symptoms of this disease take a more indolent form with an isolated abducens nerve palsy and mild chemosis and proptosis [1, 20, 47].

Thrombosis of the superior and inferior petrosal sinuses is usually a sequela of cavernous or LS thrombosis. The occlusion of the superior sinus presents as a trigeminal palsy, while the thrombosis of the inferior one is characterized by an abducens palsy [1].

Cortical veins thrombosis. Isolated thrombosis of cortical veins without associated dural sinus occlusion is infrequent (2%) [1, 20]. The most often involved are the superior cerebral veins (rolandic, parieto-occipital and posterior temporal) which empty into the SSS. This condition presents as focal deficits or seizures of sudden or progressive onset. However, if the collateral circulation is efficient there will be only an area of localized edema (that can be asymptomatic) or no parenchymal lesion at all. The neuronal lesions that may appear are mostly reversible, thus the clinical recovery is complete in some cases. Usually, thrombosis spreads to the SSS and to cortical veins on the opposite side, leading to signs of intracranial pressure and bilateral parasagittal infarct [1].

Thrombosis of the deep venous system is more frequent in children; it is much less common than dural sinus thrombosis. This condition can cause extensive thalamic and basal ganglia hemorrhagic infarcts and edema, sometimes with bilateral brain involvement [14, 20]. The clinical picture is usually severe. Most patients present with rapid neurological deterioration, manifested as stupor or coma, decerebration, decortication, signs of raised intracranial pressure, papillary changes, vertical gaze palsy, mental troubles, and motor deficits [1, 14, 19, 20]. The most common symptoms in adults are headache, nausea and vomiting, gait ataxia, neuropsychological symptoms, disturbances of consciousness, hemiparesis (that may be bilateral or alternating) and seizures. When patients survive, they often show residual signs such as abulia or memory impairment. It was reported the possibility of benign forms of galenic thrombosis [1, 20].

Venous infarctions in the posterior fossa result from thrombosis of LS, SS and the superior petrosal vein. The isolated form is extremely rare due to the abundant collateral venous drainage of the posterior structures. However, it is an important differential diagnosis in patients who has risk factors for CVT and presents with cerebellovestibular symptoms, headache, intracranial hypertension syndrome, and atypical findings on brain CT such as pan-cerebellar and vermian infarcts, cerebellar hemorrhages of irregular shapes, or with extension to the subarachnoid space and cerebellar peduncles [48]. Cerebellar veins thrombosis causing cerebellar infarction has only rarely been described. This condition is usually associated with LS thrombosis. The clinical pictures of venous and arterial cerebellar infarcts are similar, the most common signs being headache, vomiting, ataxia and unilateral dysmetria; these symptoms can be associated with a decrease in conscious level and papilledema suggesting obstructive hydrocephalus. If the thrombotic process spreads to IJV, the patients may develop cranial nerve palsies (9th and 10th cranial nerves involvement) [1, 20].

Internal jugular vein (IJV) thrombosis is, in most of the cases, a consequence of LS thrombosis extension, presenting with unilateral pulsating tinnitus or multiple cranial nerve palsies. IJV thrombosis can be rarely, accompanied by pulmonary embolism. The thrombophlebitis of the jugular vein may occur as a complication of the syndrome of tonsillopharyngitis (Lemierre's syndrome) [1, 9, 20].

The emissary veins (EV) (e.g. petrosquamosal sinus (PSS)), are residual valveless veins which connect the intracranial dural venous sinuses and the extracranial venous system. Posterior fossa EVs go through cranial apertures and participate in extracranial venous drainage of the posterior fossa venous system, in addition to IJV. EVs are usually small and have no clinical significance in healthy people; however they may become enlarged in patients with high-flow vascular malformations, IJV aplasia or thrombosis. In such cases, the clinical picture may include various craniofacial syndromes and tinnitus [49, 50].

7. Diagnosis

The diagnosis of CVT is typically based on clinical suspicion and imaging confirmation – demonstration of an occluded sinus/vein and of the thrombus [2, 14]. Patients with CVT are younger, usually female and have low frequencies of vascular risk factors (hypertension, coronary artery disease, diabetes and smoking) when compared with patients with arterial occlusive disease [20]. The clinical evolution in CVT patients is slower than in those with arterial occlusion and is characterized by headache and other signs of intracranial hypertension associated with focal neurological deficits and new seizures. The presence of hemorrhagic infarcts, especially if multiple or in no arterial vascular territories also indicates CVT [4, 20]. The highly variable clinical picture of cerebral venous disease often cause important delays in diagnosis [4].

8. Laboratory testing: thrombophilia testing

In order to establish the underlying cause of cerebral venous disease, there may be necessary several laboratory investigations [1].

Blood assay. A complete blood count, chemistry panel, sedimentation rate, measures of the prothrombin time and activated partial thromboplastin time are indicated for patients with suspected CVT. These tests may demonstrate abnormalities suggestive of a hypercoagulable state, infective, inflammatory or malignant disorders. (Class I; Level of Evidence C). A urinalysis may reveal proteinuria indicating a nephrotic syndrome. Considering that in elderly CVT patients, the proportion of cases with malignancies and hematological disorders is higher and that, sometimes, the cause of CVT is revealed only weeks or months after the acute phase, searching for an occult neoplasm is always recommended in elderly patients and idiopathic cases [1, 2, 14].

D-dimer concentrations are increased in most patients so a low level of D-dimer (<500 ng/mL) may help identify patients with low probability of CVT (Class IIb; Level of Evidence B). It is important to mention that normal D-dimer level does not exclude the diagnosis, particularly

in patients who present with isolated headache and in case of prolonged duration of symptoms (i.e. >1 week) before the test [4, 14, 20, 51].

Lumbar Puncture is indicated only if there is a clinical suspicion of meningitis. Elevated opening pressure is a frequent finding in CVT and is present in about 80% of patients. Also, there may be observed a mild lymphocytic pleocytosis, increased protein and red blood cells. The CSF is rarely (10%) entirely normal in CVT, but there are no specific CSF abnormalities associated with this condition [1, 9, 14].

Thrombophilia screening is recommended in all CVT patients, especially in those with high probability of carrying severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at CVT, CVT without a transient or permanent risk factor) [4, 14]; these tests should be performed even when another associated condition is already found because they imply a systematic family study and modify the long term management of the patients. Testing for prothrombotic conditions should include evaluation for prothrombin G20210A mutation, factor V Leiden mutation, protein C, protein S, antithrombin deficiency, antiphospholipid syndrome (lupus anticoagulant, anticardiolipin antibodies), and hyperhomocysteinemia. Testing for protein C, protein S, and antithrombin deficiency must be performed at least 6 weeks after a thrombotic event and 2–4 weeks after stopping warfarin. (IIa/ B) [2, 4, 14]. Protein C, S, and antithrombin levels may be also influenced by oral contraceptives, pregnancy, severe liver disease, L-asparaginase chemotherapy and nephrotic syndrome. The screening results should be confirmed with repeat testing and family studies [2, 4]. Other tests may include a functional plasminogen assay and qualitative testing of platelet functioning.

A diagnosis of antiphospholipid syndrome requires abnormal laboratory testing on 2 or more occasions at least 12 weeks apart because abnormal results may occur transiently due to the disease process, infection, some medications or other causes. However, if a normal result is obtain at the time of clinical presentation, the antiphospholipid antibody syndrome is ruled out [14].
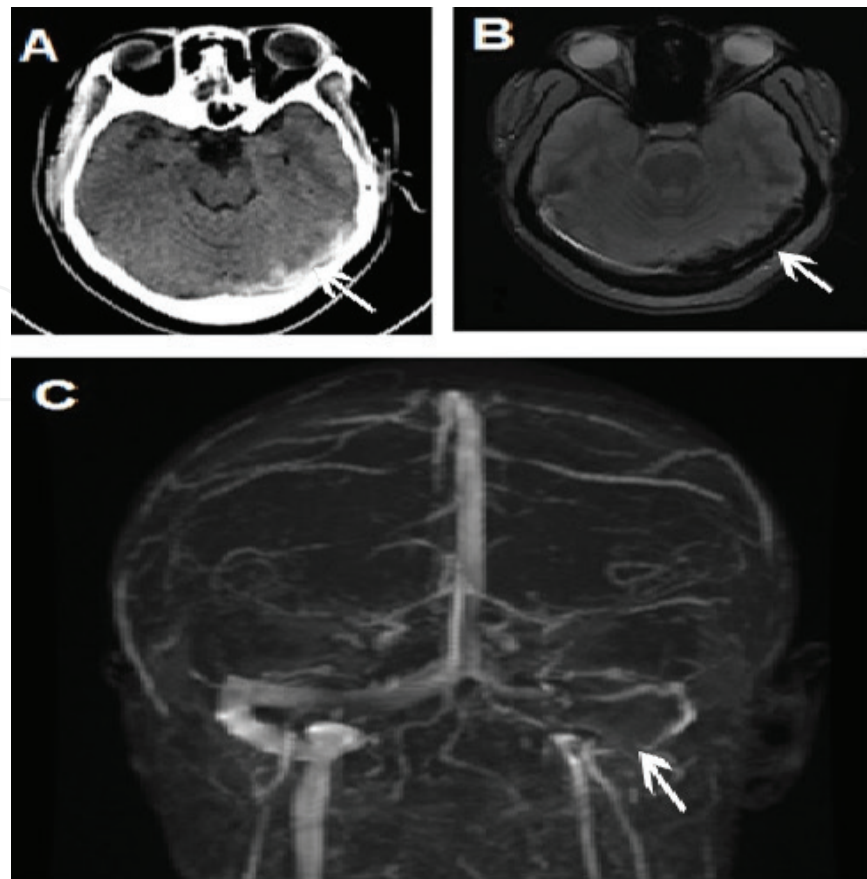
9. Imaging

The diagnosis of CVT is based on neuroimaging. The goal of this tests is to determine vascular and parenchymal changes associated with this condition (**Figure 3**) [14, 19].

Computed tomography is usually the first investigation performed in patients who present with new-onset neurological symptoms such as headache, seizure, mental alteration, or focal neurological signs [5, 14]. It is useful especially in the emergency setting because is fast and widely available [2, 52]. The place of CT scanning in the diagnostic strategy of CVT is mainly the rule out other acute cerebral disorders that CVT can imitate including arterial stroke, abscess, tumors and subarachnoid hemorrhage. Sometimes, CT identifies lesions that can themselves cause CVT such as meningioma, abscesses, sinusitis or mastoiditis [1, 4, 5].

There have been described various direct and indirect CT signs associated with CVT.

a. *Direct signs of CVT* can be founded in about 1/3 of CVT cases; they correspond to the visualization of thrombus itself and include: the "cord sign, the "dense triangle sign," and the "empty delta sign." [5, 6, 14]

Figure 3. (A) Nonenhanced computed tomography (CT) in the axial plane demonstrating spontaneous hyperdensity of the left lateral sinus (white arrow). (B) Magnetic resonance (MR) T2*SW imaging in the axial plane demonstrating left LS hyposignal (white arrow). (C) Magnetic resonance (MR) venography in the coronal plane noting absence of flow in the left LS (thrombosis of the left LS) (white arrow) [46].

The cord sign (visible on unenhanced CT scans) is found in 25% of CVT patients and is defined as a homogeneous hyperdense appearance of a thrombosed cortical or deep vein. It reflects a newly formed thrombus in a cerebral vein and is best seen within the first week of the disease. After 7–14 days, the clot becomes isodense and then hypodense. It is known that slow flow can also produce this sign, thus its specificity is considered to be rather low [1, 6, 52].

The "dense triangle sign" (seen on no contrast CT scans) was reported in less than 2% of cases; it is characterized by the hyperdense appearance of the thrombosed sinus and can be seen during the first 2 weeks of the disease. Mimicking occurs in patients with increased hematocrit or dehydrated [1, 3, 6, 9].

The empty delta sign (seen after injection of contrast agent) is present in about 35% of reported cases and only in patients with SSS thrombosis. The empty delta sign reflects a lack of contrast enhancement within the posterior 1/3 of the SSS that is surrounded by contrast enhancement of the wall of the sinus due to the presence of collateral tributaries. It is absent when the test is performed either in the first 5 days or more than 2 months after onset of symptoms. An early division of the SSS can appear as a false delta sign [1–5, 20].

b. *Indirect signs of CVT* are more frequent and include the following findings. Intense contrast enhancement of the falx and tentorium or areas of gyral enhancement can be observed in

the region of a thrombosed dural sinus; it is seen in 20% of CVT cases [1, 5, 20]. The presence of brain edema with small, compressed ventricles can be found in 20–50% of CVT patients. This sign can be difficult to differentiate from normal brain, especially in young patients. The opposite finding (enlarged ventricles) does not exclude the diagnosis considering that it can be associated with cerebellar vein thrombosis [1, 20]. Cortical veins may appear dilated on contrast-enhanced scans due to dilatation of collateral tributaries [20]. Localized or diffuse areas of white matter hypodensity without contrast enhancement are present about 75% of cases; they suggests cerebral edema (sometimes associated with mass effect) or venous infarction which usually do not respects the arterial boundaries. Venous infarcts can be unilateral or bilateral, single or multiple; venous infarcts are usually hemorrhagic, being described on CT as spontaneous hyperdensity (10–50%); In most CVT patients, parenchymal lesions manifests on CT as large subcortical often multifocal hematomas and petechial hemorrhages within large hypodensities. No hemorrhagic venous infarcts are considered to be equally frequent. In serial CT scans some lesions may disappear ("vanishing infarcts") and new others may appear [1, 5, 20]. In less than 1% of cases, CVT is associated with a subarachnoid hemorrhage, usually found in the vicinity of the venous occlusion. Subdural hematomas are also infrequent [1, 2, 14, 20].

Particular forms of CVT may present with some distinctive features. On post-contrast CT scans of patients with cavernous sinus thrombosis can be found multiple irregular filling defects with bulging cavernous sinuses and enlarged orbital veins. Cerebellar venous infarction can be associated with hydrocephalus and compression of the forth ventricle. In case of deep venous system thrombosis the characteristic findings may include: the presence of bilateral hypodensities involving the thalami and basal ganglia, hyperdensities in these same regions (hemorrhages or hemorrhagic infarction), severe edema with compression of the third ventricle and hyperdense appearance of the occluded sinuses and deep veins on unenhanced CT scans [1, 20].

It is important to emphasize that CT is normal in up to 30% of CVT cases and most of the findings are nonspecific. Anatomic variability of the cerebral venous system makes CT diagnosis of CVT insensitive, results on no contrast head CT being abnormal only in 30% of CVT cases. Therefore, a negative CT examination will not exclude a diagnosis of CVT; in suspected cases, an MRI or angiographic examination is necessary for further confirmation [4, 5, 14, 53].

Nevertheless, the distribution of the parenchymal abnormalities, including diffuse edema, bilaterally infarcts or hemorrhages, predominance of hemorrhagic changes and the presence of a lesion which crosses usual arterial boundaries should always raise the suspicion of CVT [14, 20].

CT angiography (helical CT venography) with bolus injection of contrast material gives excellent details of venous circulation anatomy and pathological changes including: filling defects in the occluded sinus or veins, sinus wall enhancement, increased collateral venous drainage and tentorial enhancement [1, 5]. CT venography is especially useful in the acute setting because it provides a rapid (it can be performed immediately after brain CT) and reliable method for detection of CVT, particularly in patients with contraindications to MRI. Also, it allows the diagnosis of sub-acute or chronic CVT because it can detect thrombus of

heterogeneous density. CT venography is less invasive, less expensive and offers a better visualization of the cavernous and inferior sagittal sinuses then intra-arterial angiography; it is comparable to MR venography for the diagnosis of cerebral venous thrombosis. Limitations of CT venography include: limited visualization of skull base structures in 3D display, contrast allergy, contrast nephropathy and radiation exposure, which may limit its use in pregnant women, children and patients with renal failure [4, 5].

Magnetic resonance imaging. The combination of MRI showing the thrombosed vessel and MR venography (MRV) demonstrating the no visualization of the same vessel is currently the most sensitive (90%) method to confirm the diagnosis of CVT in the acute, subacute, and chronic phases. Therefore, the combination of an alteration of signal intensity in a dural sinus and a corresponding absence of flow on MRV supports the diagnosis of CVT [2, 4, 14, 53, 54].

MRI pathological signs in patients with CVT include those seen in the venous channels and those seen in the brain parenchyma [14].

The signal intensity of the thrombus on T1- and T2-weighted MR images varies according to the age of the thrombus [5, 6, 14]. In the acute stage (0–5 days), flow void is absent and the occluded vessel appears isointense with brain parenchyma on T1-weighted and hypointense on T2, due to the appearance of deoxyhemoglobin in red cells within the thrombus. In the sub-acute phase (6–15 days), the absence of flow void persists, but, the thrombus appears hyperintense in both T1- and T2-weight images due to the accumulation of methemoglobin in the venous thrombus. These intermediate pattern (increased signal on T1- and T2-weighted images) is characteristic for CVT. In chronic stages, recanalization of the previously occluded vessel results in reappearance of the flow void; the thrombus can be heterogeneous with variable intensity on T2-weighted and isointense on T1-weighted images, related with the presence of the deoxygenated hemoglobin and methemoglobin products. At 6 months, more than 2/3 of cases still show some heterogeneous localized signal abnormalities which can persist for years [1, 4, 53, 54].

MRI shows a variety of focal parenchymal changes in up to 40% of patients; they include: edema, brain swelling and/or hemorrhage. The presence of edema is suggested by increased signal on T2-weighted images and isointense or hypointense signal on T1- weighted images. An increased signal in both T1- and T2-weighted images is indicative for parenchymal hemorrhage and can be seen in about 30% of the CVT cases [1, 6, 14, 53].

The SSS thrombosis is typically associated with flame-shaped, irregular areas of lobar hemorrhage in the parasagittal frontal and parietal lobes; temporal or occipital lobe parenchymal changes correspond to lateral (transverse and sigmoid) sinus thrombosis; deep parenchymal abnormalities, including thalamic hemorrhage, edema, or intraventricular hemorrhage are suggestive for thrombosis of the vein of Galen or SS [6, 14].

After contrast (gadolinium) administration, marked contrast enhancement and flow voids may be observed within the thrombosed sinuses, slow flow in dural and intrathrombus collateral channels or recanalization [2, 5].

Diffusion-weighted imaging (DWI) allows the direct visualization of the clot as a high signal intensity within the affected vein or dural sinus. However, the major interest of DWI is to

show, in the venous infarcts, a diffusion pattern significantly different from that in arterial infarcts. The DWI most common pattern of brain lesions in CVT is a heterogeneous signal intensity with normal or increased apparent diffusion coefficient (ADC) corresponding to vasogenic edema, and thus, markedly different from that of arterial infarcts [1, 5, 19].

*Echo-planar T2 susceptibility weighted imaging (T2*SW) sequences* are useful in the diagnosis of isolated cortical venous thrombosis and during the very early days of acute CVT when T1 and T2 are less sensitive. This diagnosis technique identifies the intraluminal thrombus as a hypointense area [2, 5, 19].

Hydrogen 1 magnetic resonance spectroscopy (MRS) shows a normal N-acetyl aspartate (NNA) peak and a small lactate peak, suggesting that the functionally impaired neurons are still viable in CVT; these findings also, emphasize the difference between venous and arterial infarcts [1].

The MRI advantages in CVT diagnosis include sensitivity to blood flow, ability to visualize the thrombus itself and noninvasiveness. However, its use is limited in some situations, such as comatose patients or in dubious cases (e.g. isolated cortical vein thrombosis), when intra-arterial angiography is necessary to confirm the diagnosis [1, 5].

Magnetic resonance venography (MRV) has become the imaging modality most widely used in CVT diagnosis, being easily repeatable and noninvasive [1, 3, 20]. Several methods can assess venous or dural sinus flow: two-dimensional time-of-flight (2D-TOF), three dimensional time-of-flight (3DTOF) and phase contrast; contrast enhancement MR venography with elliptic centric ordering is a newer technique which allows superior assessment of smaller venous channels [1, 5, 20]. The 2D-TOF technique is the most commonly used method for the diagnosis of CVT, showing abnormalities in the normal flow signals, no opacification of sinuses and collateral venous channels; the absence of flow signal indicates a complete intra-luminal thrombosis [1, 14, 20]. The indirect signs of cerebral venous disease include delayed emptying, collateral venous pathways, venous dilation and tortuous cortical collateral veins (corkscrew veins) [3]. Contrast-enhanced MRV is also useful in distinguishing anatomic variants such as a hypoplasic sinus from CVT. Nevertheless, MRV has a limited role in diagnosing partial thrombosis, cortical vein and cavernous sinus thrombosis; also it has limited utility in patients with renal disease (risk of nephrogenic systemic fibrosis) [1, 3, 4]. In order to assess the recanalization of the occluded cortical vein/sinuses it is recommended to perform a follow-up CT or MR venography at 3–6 months after diagnosis (IIa/ C) [1, 14].

Cerebral angiography and direct cerebral venography are invasive diagnostic techniques, being reserved for rare situations when the clinical suspicion of CVT is high, but MR or CT venography results are inconclusive or if an endovascular procedure is planned. For example, it may be useful in cases of isolated cortical vein thrombosis or when is necessary to exclude a dural arteriovenous fistula or distal aneurysm [4, 5, 14].

Cerebral angiography. The partial or complete lack of opacification of veins or sinuses is the best angiographic evidence of CVT. Other signs present and suggestive for venous occlusive disease are: venous congestion with dilated cortical, scalp, or facial veins, dilatation of collateral venous channels ("corkscrew" veins) and reversal of venous flow [1, 14, 20]. CVT is easy to recognize on angiography when it affects the posterior or whole SSS, both LSs or the

deep venous system, but it can be confused with hypoplasia when the anterior third of the SSS or the left LS are occluded. In such cases, in order to establish the diagnosis of CVT is necessary to find additional evidences: involvement of another sinus or delayed emptying and dilated collateral veins in occlusion of the anterior part of the SSS and absence of filling of the whole sinus or its sigmoid portion in LS thrombosis. The presence of collateral veins pathways usually indicates SSS thrombosis and is found in about 50% of CVT cases [1]. The limitations of this technique include the facts that it does not show the thrombus itself, has a traumatic effect, is associated with the usual risk of complications during surgery, involves a certain amount of radiation, requires a higher technical competency and may only be performed in a qualified hospital. Also, certain individuals are allergic to the iodine contrast material [1, 53].

Direct cerebral venography is usually performed during endovascular therapeutic procedures; it allows the visualization of the intraluminal thrombus either as a filling defect within the lumen (no occlusive thrombosis) or as complete no filling (occlusive thrombosis). Complete thrombosis may also present a "cupping appearance" within the sinus [14].

10. Management

The treatment of cerebral venous disease focuses on a combination of symptomatic, etiologic and antithrombotic medications on a case-by-case basis. The therapeutic measures used in clinical practice are based on anticoagulation, control of seizures, and management of increased intracranial pressure. Any underlying cause or risk factors should be managed appropriately. Patients with CVT should be admitted in a stroke unit and the treatment, started as early as possible [1, 9, 15].

10.1. Acute phase therapy

10.1.1. Antithrombotic treatment

There is now ample evidence that heparin is safe even when CT or MRI demonstrate a hemorrhagic lesion. The aims of antithrombotic treatment in CVT are to recanalize the occluded sinus or vein, to combat the propagation of the thrombus, and to treat the underlying prothrombotic state-in order to prevent venous thrombosis in other parts of the body-and to prevent the recurrence of CVT [1, 5, 19].

A meta-analysis shows that, with heparin, there is an absolute risk reduction in mortality of 14% and in death or dependency of 15%, with relative risk reduction of 70 and 56%, respectively [1, 55]. In ISCVT cohort, more than 80% of the patients were treated with anticoagulants, indicating a consensus on the efficacy and safety of anticoagulation in the acute phase of CVT [16]. Despite the fact that new or increased hemorrhages do indeed occur after heparin treatment for cerebral venous disease, their frequency is low. The risk for intracranial and systemic hemorrhages is as well, low and such hemorrhages did not influence the outcome. Anticoagulant therapy is also safe in children [5].

Thus, current guidelines recommend immediate treating patients with acute CVT with heparin, as a bridge to oral anticoagulation with a vitamin K antagonist. Heparin is either subcutaneously administered low–molecular weight heparin (LMWH) (180 anti-factor Xa U/kg/24 h administrated by two subcutaneous injections daily) or dose adjusted intravenous (IV) unfractionated heparin (UFH), titrated to an activated partial thromboplastin time (APTT) of twice the upper limit of normal. This recommendation also applies to patients with an intracerebral hemorrhage at baseline (Ia/A). LMWH should be preferred in uncomplicated CVST cases considering that LMWHs have a longer-life, more predictable clinical response and less interaction with platelets compared with standard heparin. However, this recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or in cases when fast reversal of the anticoagulant effect is necessary (e.g. patients who have to undergo neurosurgical intervention) [2, 15, 19, 51].

Although the majority of patients recover with anticoagulant therapy, a subset of patients with CVT have poor outcomes despite anticoagulation. Local IV thrombolysis (catheter-directed fibrinolysis), with or without mechanical thrombectomy are invasive therapeutic procedures which have been considered only in acute patients with CVT and large hemorrhagic infarcts, without impending herniation, who deteriorate despite adequate anticoagulation and symptomatic treatment (III/B) [1, 2, 19]. These procedures may be performed in selected expertise centers in interventional radiology [5, 19].

Thrombolysis can be done through peripheral veins or through selective cannulation. In direct catheter thrombolysis, a microcatheter and microguide wire are sent to the occluded dural sinus through a guiding catheter from the jugular bulb. Mechanical manipulation of the thrombus with the guidewire can potentially reduce the amount of fibrinolytic agent required for sinus recanalization [14]. *Balloon-assisted thrombolysis* may be more efficient because the inflated balloon may reduce washout of fibrinolytic agent, thus lessening the dose used and the risk of its eventual side effects. The balloon may be used to perform partial thrombectomy before pharmacological thrombolysis [14]. It is important to emphasize that, currently there is no evidence to support the routine use of thrombolysis, considering that both local urokinase and r-TPA carry an undeniable risk of hemorrhagic complication and may require continuous infusion [1, 5, 15, 56, 57].

Catheter thrombectomy. Currently there is no endovascular device specifically designed to treat CVT [57]. *The AngioJet system*, which was designed for use as a thromboaspiration catheter in cardiovascular indications, is not sufficiently supple to be easily passed through the tortuous intracranial sinuses. Although, the walls of the sinuses are thick enough to allow catheterization, the AngioJet device should be removed after partial recanalization of the thrombosis and follow-up with additional local thrombolysis [14, 58, 59]. *The Merci* retrieval is a snare-type device that removes thrombus in a corkscrew fashion using a series of coiled wires. This device may be used in combination with local thrombolysis in order to avoid damaging the wall or trabeculae of the dural sinus [58, 60]. *The Penumbra System* is a new-generation neuroembolectomy device helpful mainly in arterial thrombus extraction [14, 61, 62]. It uses a separator wire under vacuum suction in order to destroy the clot. In CVT patients, it may be performed in combination with continuous infusion of local urokinase [58, 63] or with an

adjuvant balloon angioplasty (without local thrombolysis) [58, 64]. The risks associated with the Penumbra System use in CVT treatment are similar to those seen with the Merci and AngioJet systems [14].

10.1.2. Symptomatic treatment

Early initiation of antiepileptic drugs is recommended in patients with acute CVT presenting a single seizure with or without supratentorial lesions, in order to prevent early recurrent seizures. The routine use of antiepileptics in CVT patients without seizures is not recommended (III/C) [14, 19, 51]. However, antiepileptic drugs could be considered as an option for patients with either acute seizures, supratentorial lesions or motor deficits. Any of the major antiepileptic agents can be used, however valproate is preferred to phenytoin and carbamazepine because it causes less interference with oral anticoagulants. If it is not tolerated other antiepileptic (lamotrigine, levetiracetam) can be used [1, 5, 51].

10.1.3. Treatment of intracranial hypertension

Brain swelling is observed in about 50% of all CVT on CT scan, however minor brain edema needs no treatment than anticoagulants, considering that heparin improves the venous outflow and, thus reduce intracranial pressure in most patients. Antiedema treatment is required in only 20% of patients [15, 19].

General recommendations in the acute stage of CVT include: elevating the head of the bed, osmotic diuretics (e.g., mannitol), intensive care unit admission with sedation, hyperventilation to a target $PaCO_2$ of 30–35 mmHg and ICP monitoring [5]. In cases associated with *severe headache* with or without papilledema, the symptoms can be ameliorate with analgesics or through a therapeutic lumbar puncture (LP) (before starting heparin) when not contraindicated by parenchymal lesions. Administration of a diuretic as acetazolamide or furosemide is a therapeutic option [1, 5]. In patients with isolated intracranial hypertension *and threatened vision*, a LP should be performed with sufficient CSF removal to obtain a normal closing pressure. Acetazolamide may be an option in patients with papilledema [15, 19]. If severe headaches persist or vision continues to deteriorate despite the correct treatment, there should be considered shunting procedures (lumboperitoneal, ventriculoperitoneal shunts or optic nerve fenestration) [5, 15]. If *consciousness becomes abnormal*, mannitol is usually added; however, shunting or barbiturate-induced coma might be necessary in more severe cases [1].

In patients with CVT and large hemorrhagic infarcts, with imminent unilateral hemispheric herniation, decompressive surgery, such as hemicraniectomy or hematoma evacuation can be life-saving, with improved clinical outcomes (III/B) [2, 4, 19].

10.1.4. Etiologic treatment

In CVT patients with a suspected local or systemic infection the treatment should include administration of the appropriate antibiotics and the surgical drainage of infectious sources. (I/C) [1, 14].

10.2. Management after the acute phase

In order to prevent recurrent CVT and other venous thrombosis, *the anticoagulation* should be continued after the acute phase of CVT [19]. There are no controlled data on the required duration of oral anticoagulation. Thus, the guidelines recommend anticoagulation with an oral vitamin K antagonist and a target INR between 2 and 3 for 3–6 months in patients with provoked CVT (septic thrombosis) and 6–12 months in patients with idiopathic CVT and in those with "mild" thrombophilia. Patients with recurrent CVT, deep vein thrombosis, or pulmonary embolism complicating CVT or initial CVT in the setting of "severe" thrombophilia (homozygosity for prothrombin gene mutation 20,210 or factor V Leiden; combined thrombophilias; deficiencies of antithrombin, protein C, or protein S; or antiphospholipid antibodies), should be considered for indefinite duration anticoagulation (III/B) [2, 4, 17, 19].

Prevention of seizures. Seizures occur in 11% of the patients, more so if the patient had seizures in the acute phase or had a hemorrhagic parenchymal lesion. Such patients can be placed on antiepileptic drugs to prevent seizure recurrence [19]. Then, anticonvulsants can be progressively discontinued 1 year after CVT in patients with normal EEG and no recurrent seizures [1].

Acetazolamide might be helpful in patients with milder pressure elevation found during follow-up, but if *visual acuity decreases and the headaches* persist despite to these measures, CSF shunting procedures should be considered [9, 19].

It is important to know that steroids are not useful and should be avoided in patients with cerebral venous disease, unless they are needed to treat an underlying disease. (IIa/B). Current guidelines recommend using steroids in patients with acute CVT and Behcet's disease or other inflammatory diseases (e.g. SLE) to improve outcome [2, 19, 51].

Contraception and future pregnancies. Anticoagulation for CVT during pregnancy and early in the puerperium consists of full-dose LMWH in the majority of women, considering that, in contrast to UFH, LMWH is not associated with teratogenicity or a higher risk of fetal bleeding (IIa/C) [5, 14, 17]. If there is needed, a regional anesthesia should be performed 10–12 h after the last prophylactic dose of LMWH and 24 h after the last therapeutic dose of LMWH. If there are used prophylactic UFH doses (5000 units twice daily), regional anesthesia can be safely placed, but in cases which require higher doses (10,000 units twice daily or greater), an individual assessment is usually necessary [65–67].

The anticoagulant therapy with LMWH or vitamin K antagonist with a target INR of 2.0–3.0 should be continued for ≥6 weeks postpartum (for a total minimum duration of therapy of 6 months) (I/C). Women who have suffered CVT in the setting of hormonal contraceptive therapy should use other contraceptive methods apart from oral or parenteral agents. Emergency contraception and hormonal replacement therapy are also contraindicated. Women with a history of CVT while receiving OC, during pregnancy, or during the postpartum period have an increased risk of recurrence during subsequent pregnancies. Thus, prophylactic anticoagulation with LMWH during future pregnancies and the postpartum period is reasonable for women with previous history of CVT (IIa/C) [4, 5, 17]. It is essential to know that CVT and pregnancy and puerperium-related CVT are not contraindications to future pregnancy.

Nevertheless, further investigations regarding the underlying cause and a consultation with a hematologist or maternal fetal medicine specialist are indicated. Women of fertile age with past CVT should be advised not to become pregnant while taking an oral anticoagulant because of its teratogenic effects [5, 17, 19].

11. Prognosis

The clinical course of CVT is unpredictable and the individual prognosis is difficult to predict, but the overall vital and functional prognosis of this condition is far better than that of arterial stroke, with about two-thirds of patients recovering without sequelae [5, 17, 19]. In a meta-analysis of 1180 patients with CVT, the mean 30-day mortality rate was 5.6%, that of death at the end of follow-up was 9.4% and that of complete recovery was 88% [4, 5, 68]. Approximately 4% of patients with CVT die within 30 days from symptom onset [14, 16]. The primary cause of death in acute CVT is transtentorial herniation secondary to a large hemorrhagic lesions, followed by herniation due to multiple lesions or to diffuse brain edema. Other causes of early death include status epilepticus, medical complications, and pulmonary embolism [4, 14, 19]. A high mortality rate within the first months is associated with depressed consciousness, altered mental status, thrombosis of the deep venous system, right hemisphere hemorrhage and posterior fossa lesions [9, 14, 19].

According to ISCVT results, about 1/4 of CVT patients deteriorate after their initial presentation, developing seizures, coma, worsening of or a new focal deficit, increased headaches or vision loss. Among these patients, about 1/3 will have new parenchymal lesions if neuroimaging is repeated [2, 9, 16].

Predictors of poor outcome derived from the ISCVT cohort are: central nervous system infections, malignancy, deep cerebral venous system thrombosis, hemorrhage at admission CT/MRI, GCS score on admission less than 9, poor mental status, age older than 37 years and male gender [16, 51]. Death after the acute phase is predominantly due to the underlying conditions, in particular malignancies [2, 19]. Based on this results, the ISCVT study group developed a risk score for poor outcomes which range from 0 (lowest risk) to 9 (highest risk) with a cut-off ≥3 points indicating a higher risk of death or dependency at 6 months. Two points were assigned for the presence of malignancy, coma, or thrombosis of the deep venous system and 1 point for male sex, presence of decreased level of consciousness, or intracerebral hemorrhage (ICH) [14, 69].

If the patient with CVT survives, the prognosis for recovery is much better (about 80%) than for patients with arterial stroke. A minority (10%) of patients are found to have permanent neurological deficits by 12 months of follow-up. About 44% of the CVT patients have some degree of handicap or significant cognitive impairment after 1–4 years [1, 4, 16]. Sequelae of CVT include cognitive and motor impairments, seizures, headaches, visual loss and an increased risk for further venous thrombotic events. Also, approximately one half of survivors feel depressed, anxious or experience minor cognitive or language deficits [4, 5]. Residual epilepsy has been reported in 10% of the patients. Other thrombotic events such as

deep vein thrombosis and pulmonary embolism occur in about 5% of patients and mostly within the first year [4, 16]. The risk of VTE is increased in patients with severe thrombophilia. Recurrence of CVT is rare (2.8%) and tends to occur within the first year of evolution, especially after anticoagulation discontinuation [4, 17]. Severe visual loss due to intracranial hypertension is infrequent [5]. It was suggested that LS thrombosis can later induce arteriovenous malformations affecting the transverse sinus [1].

The CVT associated with postpartum state has a survival rate of 90% [1, 36]. It is considered that the absence of sex-specific risk factors is a strong and independent predictor of poor outcome in women with CVT [17]. The large majority (88%) of the pregnancies ends in normal births, the remaining being prematurely terminated by voluntary or spontaneous abortion; nevertheless, the rate of spontaneous abortion was found to be higher in CVT female patients [5]. In neonates, the functional outcome is usually normal if asphyxia is not associated [1].

It has been estimated that recanalization of the thrombosed cerebral vein and sinus occurs in 40–90% of CVT patients, mostly within the first 4 months, being limited thereafter [4, 5, 9]. The deep venous system and the cavernous sinus have a higher rate of recanalization; the lowest rates were observed in LS thrombosis. Recanalization of the occluded sinus is not related to outcome after CVT [5, 9, 14].

Author details

Dragoş Cătălin Jianu[1,2]*, Silviana Nina Jianu[3], Georgiana Munteanu[2], Flavius Traian Dan[2] and Claudia Bârsan[2]

*Address all correspondence to: dcjianu@yahoo.com

1 Department of Neurology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

2 Department of Neurology, Clinical Emergency County Hospital, Timisoara, Romania

3 Department of Ophthalmology, Military Emergency Hospital, Timisoara, Romania

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