Epidemiology, diagnosis and treatment of cerebral venous thrombosis
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General introduction and outline of the thesis
Historical perspective

Cerebral venous thrombosis (CVT), also known as cerebral venous and sinus thrombosis or dural sinus thrombosis, is considered both a distinct type of stroke (by neurologists) and a special kind of thrombosis (by internists). In their classic monograph on CVT, Kalbag and Woolf describe their search for the first report of CVT in the literature. Giovanni Battista Morgagni, an 18th century Italian anatomist and pathologist, did study the cerebral sinuses, but it is uncertain if he differentiated between ante- and post-mortem thrombosis. Kalbag and Woolf attribute the first definite description of CVT to the French physician Ribes, who, in 1825, described a patient with severe headache and epilepsy due to thrombosis of the superior sagittal and lateral sinuses. The first case of puerperal CVT dates back to 1828, when John Abercrombie, physician to King George IV, published a detailed report of a 24 year old woman who developed headaches and seizures two weeks after an otherwise unremarkable delivery. She died of a status epilepticus after a short sickbed (despite treatment with repeated bloodletting). Post-mortual examination of the brain showed thrombosis of the superior sagittal sinus and cortical veins. Abercrombie also appears to be the first to have recognized that cerebral venous thrombosis may be accompanied by subarachnoid hemorrhage.

In the following decades many clinical studies on CVT were published, mostly case reports or small case series, apart from an occasional review of the literature. A paper by Ducrest, published in 1847, deserves mentioning because he seems to be the first to differentiate between thrombosis of the cerebral veins with or without thrombosis of the cerebral sinuses. The latter form is now usually termed isolated cortical vein thrombosis. In the second half of the 20th century, larger single center studies were published, which provided a broader insight into the variable clinical manifestations and risk factors associated with CVT. Of note are the series by Krayenbuhl, Huhn, Bansal, Bousser, and the previously mentioned series by Kalbag and Woolf. Multi-center studies with data of more than 100 patients have been published in the last 25 years, the largest of which are the ‘international study on cerebral vein and dural sinus thrombosis’ (ISCVT, 624 patients) and an Indian (612 patients) and Italian (706 patients) registry.
Epidemiology and risk factors

The first estimations of the incidence of CVT were based on autopsy series. Based on an estimated mortality rate of 20-50% at that time, extrapolation of these values gave an incidence of about 0.1 to 0.2 cases per 100,000. If pediatric cases are excluded, this estimate decreases to 0.05-0.1 per 100,000. Recently performed population based studies provided a more than 10-fold higher estimate of the incidence among adults (1.2-1.3 per 100,000). This increase in incidence is most likely explained by the improvement in diagnostics, which has led to the identification of less severe cases.

Most adult patients with CVT are in their thirties or forties and less than 10% are older than 65. Among children, CVT predominantly occurs in neonates and is often associated with perinatal complications or dehydration. In young and middle aged adults – but not children or elderly – CVT is three times more common among women than men. This skewed sex ratio is the result of gender-specific risk factors: oral contraceptives, pregnancy and puerperium. A large number of other risk factors have been associated with CVT. Many of these are general risk factors for thrombosis, such as genetic thrombophilia, antiphospholipid syndrome, inflammatory disorders, and malignancies. Local conditions of the head and neck may also cause CVT, including trauma, neurosurgical interventions and infections (e.g. otitis, mastoiditis and meningitis). Although at least one risk factor is identified in most patients, in 10 to 20% no risk factor can be identified.

Pathophysiology

Two pathophysiological mechanisms can be distinguished in CVT: thrombosis of the major cerebral sinuses and thrombosis of the cortical veins. The cerebral sinuses (figure 1), besides draining blood, are also essential for drainage of cerebrospinal fluid, a process mediated by the arachnoid villi. These villi are small protrusions of the arachnoid mater into the cerebral sinuses and facilitate transport of cerebrospinal fluid from the subarachnoid space to the blood. Arachnoid villi are also known by their eponym Pacchioni’s granulations. Antonio Pacchioni, who lived from 1665 to 1726 and was a friend of the previously...
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mentioned Morgagni, applied the recently discovered microscope to study the coverings of the brain. He published his description of arachnoid villi in 1705 and believed they were glands that secreted lymph to lubricate sliding movements between the brain and meninges. Occlusion of the cerebral sinuses blocks transport of cerebrospinal fluid through the arachnoid villi. This causes intracranial hypertension, which leads to headache and – less frequently – papilledema, decreased visual acuity and sixth nerve palsy. If one or more of the cerebral sinuses are blocked, outflow of blood (and cerebrospinal fluid) must deviate to an accessory route. Such routes include the vertebral plexus and the facial vein, the latter of which is accessible either through the cavernous sinus and the superior ophthalmic vein or the pterygoid venous plexus.

Figure 1 Frequency of thrombosis of the major cerebral sinuses.

The frequencies of thrombosis in the various sinuses are given as percentages and are based on data from the ISCVT study. In most patients, thrombosis occurs in more than one sinus. Reproduced with permission from “Stam J. Thrombosis of the Cerebral Veins and Sinuses. N Engl J Med 2005;352:1791-1798”, Copyright Massachusetts Medical Society.
The second pathophysiological mechanism, occlusion of a cortical vein, restricts the drainage of blood from the adjacent brain tissue. Depending on the extent of the thrombus and the availability of venous collaterals, obstruction of a cortical vein causes an increase in venous and capillary pressure and breakdown of the blood-brain barrier.\textsuperscript{22, 25, 26} This process can result in two types of macroscopic parenchymal lesions: localized cerebral edema and intracerebral hemorrhages, which both occur in approximately 40\% of patients and often simultaneously. In the literature, these lesions are often termed \textit{venous infarct} (figure 2), but this term is controversial because it implies irreversibility.\textsuperscript{27} MRI studies have shown that in approximately half of patients with CVT associated lesions, the edema is vasogenic and thus potentially reversible.\textsuperscript{28, 29} Moreover, even lesions with decreased ‘apparent diffusion coefficient’ (ADC) values in the acute phase – suggesting cytotoxic edema – have sometimes resolved over time.\textsuperscript{30}

**Figure 2 Parenchymal lesion in CVT**

Axial non-contrast enhanced CT scan of a patient with CVT showing a parenchymal lesion in the right hemisphere with hypodense (edema) and hyperdense (hemorrhage) areas.
Clinical manifestations and diagnosis

The most common clinical manifestations of CVT are shown in table 1.11 Most of the key signs and symptoms were already recognized by physicians in the 1800’s: headache, seizures and decreased consciousness. The relation between visual disturbances and CVT was first noted by the British physician Hawthorne, who reported a female patient with severe headache, diplopia and blurred vision. At examination she had abductions paralysis of the left eye and bilateral swelling of the optic discs.31 These symptoms can be caused by intracranial hypertension, which is a well known clinical syndrome associated with CVT. Focal neurological deficits, such as hemiparesis, aphasia, hemianopia and cognitive symptoms, are caused by localized cerebral lesions due to venous thrombotic occlusions. Seizures occur in 40% of patients with CVT, much more than in arterial stroke. Among patients with parenchymal brain lesions this percentage is even higher, up to about 60%.11,32

Table 1: baseline symptoms and signs of CVT

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>89%</td>
</tr>
<tr>
<td>Visual loss</td>
<td>13%</td>
</tr>
<tr>
<td>Papilledema</td>
<td>28%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>14%</td>
</tr>
<tr>
<td>Aphasia</td>
<td>19%</td>
</tr>
<tr>
<td>Paresis</td>
<td>37%</td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>39%</td>
</tr>
<tr>
<td>Coma</td>
<td>5%</td>
</tr>
</tbody>
</table>

Derived from the ISCVT study.11

There are three imaging techniques to diagnose CVT during life: MRI with MR-venography, CT-venography and conventional cerebral angiography.33 Cerebral angiography is the gold standard, but it is rarely used because it is time-consuming and carries a small, but non-negligible risk of stroke. MRI is the most widely used technique, although CT-venography is a good – and faster – alternative with similar sensitivity and specificity.34 MRI does have the advantage that it allows better visualization of parenchymal lesions and that it does not require ionizing radiation or intravenous contrast. Therefore, in children, pregnant women, and patients with contrast allergy or renal failure MRI is preferred.
D-dimer measurements are often used in the diagnostic work-up of patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE). Large studies have shown that a low D-dimer concentration in a patient with a low or intermediate clinical probability of DVT/PE virtually rules out these conditions, which makes additional radiological investigations redundant. The sensitivity of D-dimer concentrations to exclude CVT has been assessed in several studies. A recent meta-analysis calculated a mean sensitivity of 94%. However, among patients with a chronic onset or isolated headache, the sensitivity is much lower (83 and 82% respectively). Since these are precisely the type of patients where D-dimer values would be helpful – since there may be no other reason to perform brain imaging in these patients – the value of D-dimer concentrations for excluding CVT is limited in daily practice. Perhaps future studies will show that a lower cut-off point or a combination of D-dimer with another biomarker increases the sensitivity enough to make the test sufficiently sensitive to rule out CVT in patients with a low prior probability.

Treatment and prognosis

“The introduction of heparin gives us an effective weapon to treat what has invariably been a fatal complication of the puerperium, and the clinician's reward for an early diagnosis will be the survival of the patient rather than the sterile pleasure of making an accurate diagnosis and confirming it in the post-mortem room” (F. Ross Stansfield, 1942, BMJ)

Stansfield, a British gynecologist, was one of the first to treat a patient with (puerperal) CVT with heparin, a few years after it became available for patients. The abovementioned quote is from the paper he published in the British Medical Journal in 1942, in which he described the favorable outcome of this patient. His decision to apply anticoagulation was inspired by his positive experience of heparin treatment in patients with venous thrombosis of the leg. Also, a similar case of CVT – without heparin treatment – had died 2 months earlier. Although the use of heparin in CVT gained acclamation in the following decades, it remained controversial for a long time. Opponents were concerned with the high incidence of intracerebral hemorrhages in CVT (before treatment) and the obvious risk of anticoagulation in these patients. Those in favor of heparin for CVT argued...
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that withholding heparin may lead to extension of the thrombosis with new venous occlusions and new hemorrhages.\textsuperscript{38} Clinical trials to solve this dilemma are difficult in a disease as rare as CVT. In order to solve this dilemma, four small randomized trials were performed in the nineties.\textsuperscript{40-43} A meta-analysis of two of these trials showed a non-significant difference in favor of heparin (Relative risk of death 0.33, 95\% CI 0.08-1.21).\textsuperscript{44} The other two trials were excluded from the meta-analysis; one because it has been published as an abstract only\textsuperscript{42} and the other because the diagnosis of CVT was established by unenhanced CT.\textsuperscript{41} Based upon the data from the meta-analysis, guidelines from both the ‘European Federation of Neurological Societies’ and the ‘American Heart Association’ now recommend anticoagulation with therapeutic dose of heparin as the primary treatment for CVT.\textsuperscript{33, 45} Nevertheless, as can be judged from recent publications, the debate on anticoagulation for CVT has not completely abated.\textsuperscript{46-49}

Endovascular thrombolysis for the treatment of CVT was first reported in the 1980s.\textsuperscript{50, 51} Since then, a myriad of case reports and small case series have been published on this matter, but no randomized trials or large prospective studies.\textsuperscript{52, 53} Because of the limited data on its efficacy and risk of complications – especially intracerebral hemorrhages – guidelines recommend to consider endovascular thrombolysis only in severe cases and for patients who deteriorate despite treatment with anticoagulation.\textsuperscript{33, 45} Two types of endovascular thrombolysis exist. In chemical thrombolysis a microcatheter is placed in the sinus upstream from the thrombus and a thrombolytic drug, usually urokinase or alteplase, is infused. The reported dosages vary greatly. For urokinase, for instance, dosages of as little as 12 thousand and as much as 12 million IU have been reported.\textsuperscript{53} If recanalisation is not achieved during the initial procedure, the microcatheter can be left in situ for continuous infusion.\textsuperscript{54} In such cases, a control venogram should be made at regular intervals to check for recanalisation. The second type of endovascular treatment is mechanical thrombectomy, which, judging from the number of publications, is increasingly used by interventionalists.\textsuperscript{55, 56} Various thrombectomy techniques have been used, such as rheolytic devices, balloon angioplasty and stents. The theoretical advantage of mechanical over chemical thrombolysis is a lower risk hemorrhagic complications, although there are no data to substantiate this claim.
Occasionally, patients develop large venous hemorrhagic infarcts which result in clinical and radiological signs of brain herniation. Based on the literature and our own experience the majority of these patients will die if left untreated.\(^{54, \text{57}}\) Endovascular thrombolysis is not beneficial in these situations, because recanalisation of the sinuses does not reverse the process of herniation. Steroids are sometimes used to reduce vasogenic edema, but there is no evidence for its efficacy.\(^{58}\) During the last decade data have amassed which suggest these patients are best treated with decompressive hemicraniectomy. In 1999, Stefini et al. reported good outcomes after decompressive surgery in 2 out of 3 patients with CVT and advanced stages of herniation (bilateral fixed and dilated pupils).\(^{59}\) Following this paper, several studies with similar results – with larger numbers of patients – have been published.\(^{60, \text{61}}\) While the publication of Stefini is often considered to be first on this matter, the beneficial effect of surgery in a subset of patients with CVT had already been observed years before, for instance by the famous Swiss neurosurgeon Hugo Krayenbühl.\(^{6}\)

Up until the first half of the 20\(^{\text{th}}\) century the prognosis of CVT was grave and the majority of patients did not survive.\(^{1}\) Still, even then some physicians argued that the disease should not be considered intractable and that spontaneous recovery and recanalisation were possible.\(^{31, \text{62}}\) In recent studies the prognosis is much better. In the ISCVT, mortality at last follow-up was 8.3\%.\(^{11}\) A recent large registry from Italy reported an even lower long term mortality of 2.8\%.\(^{63}\) Various factors may explain this decline in mortality, such as improvements in treatment and a shift in risk factors. The most important factor, however, is the same that explains the increase in incidence: the identification of less severe cases.

The majority of early deaths is directly the result of CVT, usually by transtentorial herniation due to large space-occupying lesions or generalized cerebral edema.\(^{57}\) Late deaths, on the other hand, are more frequently due to an underlying condition – especially cancer – or recurrent thrombotic events.\(^{13}\) Approximately 90\% of the surviving patients recover without sequelae.\(^{11, \text{13}}\) Between 5 to 12\% experience seizures in the chronic phase, mostly in patients who had a hemorrhagic infarct in the acute phase.\(^{54, \text{65}}\)
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Outline of the thesis

This thesis is divided into 2 parts. In the first part we describe studies on the epidemiology and diagnosis of CVT. Chapter 2 reports the results of a cross-sectional study of the incidence of CVT among hospitalized adult patients in 2 provinces in the Netherlands. We found that the incidence of CVT is considerably higher than previously believed. Chapter 3 is a post-hoc analysis of the ISCVT study, in which we examined the differences between women and men with CVT in presentation, course, and risk factors. This study showed that women with a gender-specific risk factor (oral contraceptive use, pregnancy/ puerperium or hormone replacement therapy) have a better prognosis than other female patients. In chapter 4, we report the results of a study on small juxtacortical hemorrhages in CVT. We found that juxtacortical hemorrhages are a characteristic feature of CVT and that these hemorrhages are rarely encountered in other conditions. Chapter 5 and 6 are both systematic reviews of the literature. In chapter 5 we have summarized all published cases of isolated cortical vein thrombosis. In chapter 6 we studied the decline in mortality of CVT over time.

The second part of the thesis focuses on novel developments in treatment of CVT. Chapter 7 is a narrative review of the different treatments for CVT. In chapter 8, we report the results of an international, web-based survey among stroke specialists to explore treatment variations in CVT. Chapter 9 is an update of the Cochrane meta-analysis on anticoagulation for CVT. Chapter 10 is a post-hoc analysis of the ISCVT study of the different types of heparin used for CVT. The data from this study suggest a better efficacy and safety of low-molecular weight heparin compared to unfractionated heparin. In chapter 11 we describe the rationale and design of the TO-ACT trial (Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis). The TO-ACT trial is an international randomized controlled trial which we launched in 2011 to examine the efficacy and safety of endovascular treatment for CVT as compared to standard treatment. Chapters 12 through 14 of the thesis describe the efficacy of decompressive hemicraniectomy for severe CVT cases with impending herniation. We were among the first to report this therapy for CVT (chapter 12) and have published one of the largest prospective studies on this subject (chapter 13). Chapter 14 is a retrospective multicentre registry and systematic review of individual patient
data on decompressive surgery for CVT. This study also marked the launch of an international prospective registry of decompressive surgery for CVT. Finally, in the chapter 15 we summarize the main findings of this thesis and discuss the implications for future research.
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