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Cerebral venous thrombosis: Epidemiology, clinical course, and outcome

Zuurbier, S.M.

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CEREBRAL VENOUS THROMBOSIS

epidemiology, clinical course, and outcome

YVONNE ZUURBIER

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CEREBRAL VENOUS THROMBOSIS: epidemiology, clinical course, and outcome
Susanna M. Zuurbier

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CEREBRAL VENOUS THROMBOSIS

epidemiology, clinical course, and outcome

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Susanna Maria Zuurbier

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PROMOTIECOMMISSIE

Promotor:	Prof. dr. J. Stam	Universiteit van Amsterdam
Copromotor:	Dr. J. Coutinho	Universiteit van Amsterdam

Overige leden:	Prof. dr. I.N. van Schaik	Universiteit van Amsterdam
	Prof. dr. M. Arnold	Universiteit van Bern
	Prof. dr. C.J.M. Klijn	Radboud Universiteit Nijmegen
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	Prof. dr. Y.B.W.E.M. Roos	Universiteit van Amsterdam
	Dr. M. Uyttenboogaart	Rijksuniversiteit Groningen

Faculteit der Geneeskunde

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1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare cerebrovascular condition that was first described by a French physician in the 19th century.[1] Patients with CVT have an occlusion of one or more of the dural sinuses of the brain, often in combination with cortical vein thrombosis. A small proportion of patients only have an occlusion of a cortical vein, which is termed isolated cortical vein thrombosis. CVT leads to a diminished outflow of blood and cerebrospinal fluid, which in about 50% of patients results in development of a venous infarct. In contrast to arterial infarcts, CVT mostly affects young adults and children and it is an important cause of stroke in the young.

EPIDEMIOLOGY

Two recent studies estimated that the incidence of adult CVT is approximately 1.3 per 100.000 person-years.[2, 3] Prior to these studies, the incidence of adult CVT was believed to be between 0.2 and 0.5 per 100.000 per year. This estimate was derived from an extrapolation of mortality and autopsy data from studies that were performed several decades ago.[4] Increased awareness of CVT and improved imaging techniques, especially MRI and CT-venography, are the most important explanations why these contemporary studies show a higher incidence.[2] The incidence is higher in patients aged 31-50 years (1.7 per 100.000), and especially in
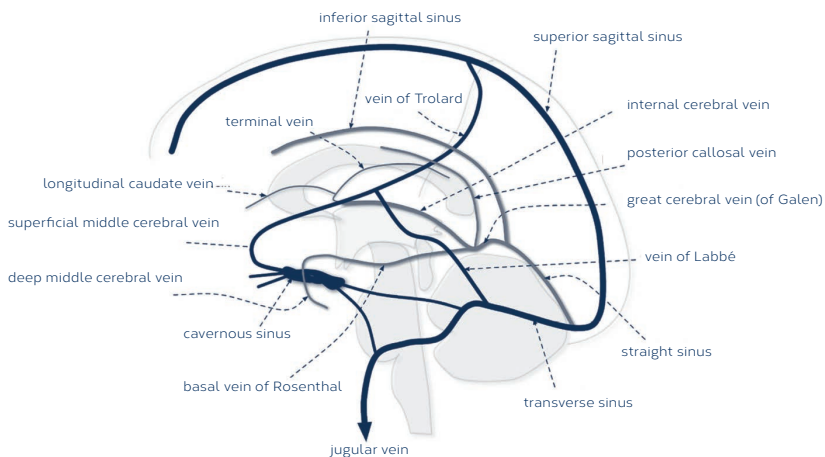
FIGURE 1. **Anatomy of the normal cerebral venous circulation.** *Reproduced with kind permission from An Atlas of Neonatal Brain Sonography, 2nd edition, by Paul Govaert and Linda de Vries, published by Mac Keith Press (www.mackeith.co.uk) in its Clinics in Developmental Medicine Series, No 182-183, 2010, 978-1-898683-56-8.*

women of that age (2.8 per 100.000).[2] In the elderly, CVT is very uncommon; less than 10% is older than 65.[5] In children, the incidence of CVT has been estimated at 0.7 per 100.000 per year, with a peak among neonates.[6]

ANATOMY AND PATHOPHYSIOLOGY

The venous drainage system of the brain can be divided into a superficial and deep part. The superficial system collects blood from the cerebral cortex and the outer 1–2 cm of white matter. Small subcortical and intracortical veins transport blood to the larger cortical veins, which in turn drain into the dural sinuses.[7, 8] Most of the cortical veins drain into the superior sagittal sinus, although some, like the inferior anastomotic vein (vein of Labbé) usually connect with the lateral sinus. The superior sagittal sinus transports blood to the transverse sinuses, of which one is often dominant. The blood flow then continues to the sigmoid sinuses and leaves the skull through the jugular veins. The deep cerebral system drains blood from the deeper white matter and basal ganglia. Blood is transported from the deep cerebral veins (internal cerebral veins, basal vein of Rosenthal, vein of Galen) to the straight sinus, which drains into the transverse sinuses (Figure 1).[9] Many anastomoses connect the different parts of the cerebral venous system and the anatomy can vary considerably from person to person.

It is helpful to differentiate between two different mechanisms in the pathophysiology of CVT: thrombosis of the cortical veins and thrombosis of the cerebral sinuses. Depending on the extent of the thrombus and the availability of venous collaterals, occlusion of a cortical vein can cause an increase in the venous and capillary pressure and breakdown of the blood–brain–barrier. This process results in localized brain edema, which can progress to venous infarction. A unique characteristic of venous infarcts is that they are often hemorrhagic. Clinically, venous infarcts cause focal neurological deficits and, often, epileptic seizures. The second pathophysiological mechanism, thrombosis of the cerebral sinuses, results in a restricted outflow of cerebrospinal fluid, leading to intracranial hypertension. Major symptoms of intracranial hypertension are headache and decreased visual acuity.[10]

RISK FACTORS

In young and middle–aged adults, CVT is three times more common in women than men. This skewed sex ratio is the result of female specific risk factors: oral contraceptive use, hormone replacement therapy, and pregnancy/puerperium.[11-14] These risk factors are generally absent in children and elderly, which explains why in these groups the sex ratio is more evenly distributed.[5, 6, 15]

Many different risk factors have been associated with CVT (Table 1). In part these overlap with risk factors for venous thromboembolism (VTE), such as genetic thrombophilia, cancer, obesity, and the previously mentioned female specific risk factors. Other risk factors, mostly those that affect the head and neck region, are specific for CVT. Examples include local infections (otitis, mastoiditis, and meningitis), head trauma, neurosurgical operation, and lumbar puncture. While septic CVT was common in the past, the frequency of infection related CVT has declined over time, probably due to improved antibiotic therapy.[10] Inherited thrombophilias that have been associated with CVT include the prothrombin G20210A mutation, Factor V Leiden mutation, protein S deficiency, protein C deficiency, increased factor VIII levels, JAK2 V617F mutation, and hyperhomocysteinemia.[16] Inflammatory bowel disease and acute lymphoblastic leukemia (ALL) are associated with both VTE and CVT, but, for reasons that are unknown, these conditions are more strongly associated with CVT than VTE.[17] In the case of ALL, the increased risk of CVT appears to be related to the use of asparaginase, possibly in combination with lumbar punctures for intrathecal methotrexate therapy. Anemia has also been associated with CVT and is present in 10-20% of patients.[15, 18] Severe obesity was recently also found to be a risk factor for CVT. Subjects with a body mass index of 40 or more have an almost 10-fold higher risk of CVT than those with a normal weight. The association between obesity and CVT is especially strong in women of reproductive age who use oral contraceptives.[19]

TABLE 1. Risk factors for cerebral venous thrombosis.

Risk factors	
Genetic thrombophilia	**Cancer**
Infections	Especially hematological malignances
Otitis/Mastoiditis	**Gender specific risk factors**
Meningitis	Oral contraceptive use
Systemic infectious disease	Pregnancy/Puerperium
Iatrogenic	Hormone replacement therapy
Catheterization jugular vein	**Medication**
Neurosurgical intervention	Steroids
Lumbar puncture	Asparaginase
Miscellaneous	Methotrexate
Anemia	**Systemic diseases**
Dehydration	Inflammatory bowel disease
Head trauma	Thyroid disease
Severe obesity	Behçet disease
Spontaneous intracranial hypotension	Systemic lupus erythematosus
Dural arteriovenous fistula	Antiphospholipid syndrome
Arteriovenous malformation	
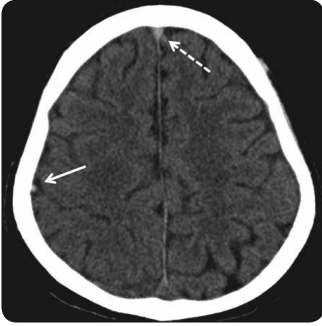
FIGURE 2. Axial non-contrast CT-scan of a 27-year-old man with CVT. *He had a history of acute lymphoblastic leukemia and presented with generalized seizures. Note the hyperdense signal in the anterior part of the superior sagittal sinus (delta sign; dashed arrow) and in one of the cortical veins overlaying the right hemisphere (cord sign; filled arrow).*

At least one risk factor can be identified in 85% of patients with CVT, and 44% has multiple risk factors.[15] The most common acquired risk factor for CVT is oral contraceptive use. The reported proportion of women with CVT who use oral contraceptives varies, depending of the country where the study was performed, but percentages of 50% or higher are not uncommon.[2, 15] Most women with pregnancy-related CVT develop symptoms in the puerperium and the risk appears to be increased up to 12 weeks after delivery.[12, 20, 21]

SYMPTOMS AND SIGNS

The clinical manifestations of CVT are variable, and the disease can be difficult to diagnose. In the International Study on Cerebral Vein and dural sinus Thrombosis (ISCVT), the median delay from symptom onset to admission was 4 days, and the median delay from onset of symptoms to diagnosis was 7 days.[15] A chronic onset of symptoms occurs in less than 10% of patients and less common in women than men.[11] The most common symptom of CVT is headache, which is found in about 90% of patients. Although any type of headache can occur, most often it is diffuse and severe. A subgroup of patients present with thunderclap headache, mimicking subarachnoid hemorrhage.[22] Presentation without headache is rare, but occurs more often in older patients, men, and in some associated conditions like isolated cortical vein thrombosis.[23, 24] Focal neurological deficits, such as paresis, aphasia, and hemianopia are found in about half of all patients, and these patients usually have a venous infarct.[15] Seizures occur in approximately 40% of patients, which is much higher than arterial stroke. A decreased consciousness can also occur, and one in 7 patients is comatose at admission, usually as a result of large venous

FIGURE 3. Axial non-contrast CT-scan of a patient with CVT. *In the right hemisphere (left side on the CT) a large hemorrhagic infarct is visible. Darker areas in the lesion indicate edema and the white areas blood.*

infarcts or bilateral edema of the basal ganglia and thalami.[15] The latter is usually due to thrombosis of the deep venous system and this can also result in behavioral symptoms such as confusion, amnesia, bradyphrenia and mutism.[25, 26]

DIAGNOSIS

Three different imaging modalities are available to diagnose CVT: CT-venography, MRI with MR-venography, and catheter angiography. Non contrast CT is insufficient to diagnose CVT, but it can show abnormalities that suggest the diagnosis. For example, a thrombus in a dural sinus or cortical vein can appear hyperdense. The latter finding is termed "cord sign" (Figure 2).[27]

The most frequently occluded sinus is the superior sagittal sinus (62%), followed by the left and right lateral sinus (each around 40%), and straight sinus (18%).[15] Although catheter angiography is still considered the gold standard, it is rarely required anymore. Given the cost and associated risk to the patient, catheter angiography should only be performed if there is doubt about the diagnosis after MRI and CT-venography. When using MRI, it is important to perform both MR-venography and regular MR sequences, because the combination of a signal alteration in the sinus and absent flow on venography is required to make the diagnosis. The precise sensitivity and specificity of MRI and MR-venography are unknown because sufficiently powered studies comparing MRI to catheter angiography have not been performed.[27] Time-of-flight and contrast-enhanced MR-venography can both be used, although the venous system can visualized better with the latter technique.[28] It is also useful to include a susceptibility weighted sequence, since this is the most sensitive technique to visualize a thrombus in a cortical vein.[29]

CT-venography is a good alternative to MRI to diagnose CVT. A small study that compared CT-venography to catheter angiography showed a sensitivity of 95% and specificity of 91% for the detection of the thrombosis of the cerebral venous system.[27] Advantages include a wide availability, quick image acquisition, and the ability to image patients with a pacemaker or other ferromagnetic devices. Disadvantages are the need for intravenous contrast material and exposure to ionizing radiation, which limits its applicability in children and pregnant women. Moreover, CT is inferior to MRI to detect parenchymal lesions and cortical vein thrombosis.[24, 30]

Parenchymal brain lesions are found in approximately 40-60% of patients with CVT, and usually consist of hemorrhagic infarcts or cerebral edema. The shape and size of hemorrhagic lesions can vary from small petechial hemorrhages to large intra-cerebral hemorrhages (Figure 3). Juxtacortical hemorrhages, which are small (<2 cm in diameter) hemorrhages that are located just below the cortex, are very typical for CVT and rarely seen in other conditions.[31] Large space-occupying hemorrhagic infarcts of the temporal lobe are usually caused by thrombosis of the vein of Labbé or one of the inferior middle cerebral veins that drain into the transverse sinus.[32]

Standard blood tests should be performed in all patients with CVT, consisting of a complete blood count, chemistry panel, prothrombin time and activated partial throm-boplastin time.[27] Routine screening for genetic thrombophilia is not recommended, since it usually does not change clinical practice, but it may be performed in selected patients with high a pre-test probability for severe thrombophilia (i.e. recurrent throm-bosis, a family history of venous thrombosis, or CVT without a risk factor).[16] Prior to screening for thrombophilia, it is advisable to consult with a thrombosis specialist. A meta-analysis showed that the sensitivity of D-dimer measurement in patients with CVT is 94%.[33] Among patients with a chronic headache or isolated headache, however, the sensitivity was considerably lower, 83% and 82%, respectively. Since these are exactly the patients in whom D-dimer measurement could be helpful, since there may be no other reason to perform brain imaging other than to exclude CVT, the value of D-dimer measurement in the diagnostic work-up of CVT is limited.

TREATMENT

Anticoagulation
The primary therapy for patients with CVT is anticoagulation with heparin in the acute phase, followed by oral anticoagulation in the chronic phase. The efficacy and safety of heparin treatment has been investigated in 3 small-randomized trials.[34-36] A meta-analysis showed a pooled relative risk of death and dependency of 0.46 (95% CI, 0.16-1.31) after heparin treatment as compared to placebo.[37] Hence, the limited data that is available suggests a beneficial effect of heparin treatment, but the difference was not statistically significant. Importantly, heparin treatment was

not associated with increased risk of hemorrhagic complications. Both low-molecular weight and unfractionated heparin are used to treat CVT, although based on data from 2 studies, low-molecular weight heparin is preferable.[38, 39] The optimal duration of anticoagulant therapy is not known, but most physicians treat for a period of 3-12 months.[40] Factors such as whether the thrombosis was provoked and the preference of the patient should be taken into account when determining the duration of treatment. In some patients, for instance in case of a recurrent thrombosis or in the presence of severe genetic thrombophilia, indefinite treatment with anticoagulation is recommended.

Endovascular treatment

During endovascular thrombolysis a catheter is introduced into the cerebral venous system, with the aim to remove the thrombus. Access is usually acquired using a transfemoral or transjugular approach, although direct puncture of a sinus through a burr hole has been reported. Thrombolysis can be achieved using chemical thrombolysis (urokinase or rt-pa), mechanical thrombectomy, or a combination of both. Although many case reports and case series have been published reporting promising results with endovascular treatment, no controlled studies have assessed the efficacy and safety of this therapy.[41, 42] Therefore, endovascular treatment should not be routinely performed in patients with CVT, although it can be considered in selected patients with a severe form of CVT or who deteriorate despite heparin treatment. Currently, there is a randomized controlled trial ongoing in which the efficacy of endovascular therapy is being assessed (TO-ACT trial).[43]

Decompressive surgery

Decompressive surgery is indicated in a small subset of patients with signs of transtentorial herniation. Clinically, these patients develop a depressed consciousness, with or without 3rd nerve palsy. Imaging will generally shows a large venous infarct with mass effect and shift of midline structures. During decompressive surgery, a hemicraniectomy (or sometimes bilateral) is performed, thereby removing the immediate threat of fatal herniation. Recent studies have shown that this procedure can be lifesaving and result in a good outcome in many patients.[44, 45] The largest retrospective study on this subject included data from 69 patients.[45] The mortality was 16%, and at follow-up 57% of the patients was functionally independent. Good outcomes have even been reported in patients with advanced stages of transtentorial herniation.[46]

Steroids

The rationale behind the use of steroids in patients with CVT is that it may reduce vasogenic edema. The efficacy of steroid treatment has only been assessed in one, non-randomised, study.[47]

Overall, there was no difference in poor outcome in patients who did or did not receive treatment with steroids, but patients without a parenchymal lesion had a worse outcome if treated with steroids. Although residual confounding may have biased the results of this study, until more data become available, the use of steroids in patients with CVT cannot be recommended, especially not in those without parenchymal lesions.

COMPLICATIONS

Seizures

As mentioned previously, seizures occur frequently in the acute phase of CVT. In patients with early seizures, most already have had their first seizure prior to diagnosis. The risk of early seizures (within 2 weeks after the diagnosis) is especially increased in patients with venous hemorrhagic infarcts.[48] There is general agreement to treat all patients with CVT who develop early seizures with anti-epileptic drugs, with the aim to prevent early recurrences.[27, 39] Late seizures and epilepsy are much less common and occur in approximately 10% of patients, although there is little data on this topic.[49] The optimal duration of treatment in patients with early seizures is unknown. Personally, we start tapering anti-epileptic drugs after 3-9 months in most patients, unless a patient has had a recurrent seizure. It is unknown if longer duration decreases the risk of late seizures.

Hydrocephalus

There is little data on the frequency of hydrocephalus in CVT. A recent study observed hydrocephalus in 14% of patients.[50] In this study, the most important risk factor for hydrocephalus was edema of the basal ganglia and thalami and, in these patients, hydrocephalus probably resulted from obstruction of the foramen of Monro. The presence of hydrocephalus was also a risk factor for poor outcome, with an associated mortality rate of approximately 30%. A direct causal relation between hydrocephalus and poor outcome, however, has not been established, and it is more likely that hydrocephalus is a marker of severe parenchymal involvement. Routine shunting procedures are therefore not recommended in patients with CVT, although this decision has to be carefully weighed in each individual patient. The fact that placement of a ventricular drain requires stopping of anticoagulation makes this decision more difficult.[50]

Intracranial hypertension

Intracranial hypertension is present in the acute phase in most patients with CVT. Besides prescription of analgesics, specific treatment for intracranial hypertension is usually not required at that stage, but frequent monitoring of the visual acuity and the presence of papilledema should be performed. This is especially important in patients with a decreased consciousness or aphasia who are unable to report

decreased vision. Acetazolamide can be prescribed to reduce the production of cerebrospinal fluid, although the effect is probably limited. Performing a therapeutical lumbar puncture is generally inadvisable, because the effect is only short lasting and it requires discontinuation of heparin treatment. We only perform a lumbar puncture in an emergency if a patient develops acute visual loss. In that situation, averting imminent blindness outweighs the small risk of hemorrhagic complications. The effect of a lumbar puncture, however, is only temporarily, and patients with a threatened vision will usually require a shunting procedure.

PROGNOSIS

The prognosis of CVT is generally good, especially compared to arterial stroke. Approximately 80% of the patients recover without disability, although many of these patients do suffer from chronic symptoms such as headache, diminished concentration and mood disorders.[15, 51, 52] These long-term symptoms often have a negative impact on the quality of life and employment status of patients.[51] Risk factors for an unfavorable outcome are: male sex, older age, an intracerebral hemorrhagic lesion, mental status disorder, coma, thrombosis of the deep cerebral venous system, central nervous system infection, and malignancy.[15] Follow-up studies have shown that recanalization occurs in about 90% of patients. In most, this process takes place early, and by 3 months, 70-80% of patients will have partial or complete recanalization.[53, 54] Whether or not there is a relation between recanalization and clinical outcome is uncertain, as the data on this issue are conflicting.[53, 54] Venous collaterals also develop in the majority of patients, but limited data on this subject do not suggest an association between collaterals and outcome.[55]

The risk of a recurrent thrombosis is around 4 per 100 person-years, although the estimates of recurrence risk vary considerably between studies. About 1/3rd of the recurrent thrombotic events are CVT and the rest are VTEs. Risk factors for the recurrence of VTE are male sex and polycythemia/thrombocytosis. Of all recurrences, the majority occurs within the first year after CVT.[56]

The mortality of patients with CVT has declined steeply over time.[57] In the past, mortality rates of 50% were not uncommon and some even believed that CVT was almost uniformly fatal.[58] In recent studies, however, the reported mortality is between 5 and 10%. Although part of the decline in mortality is probably due to better therapy and a shift in risk factors, the most important reason is that with modern imaging, less severe cases are identified. If a patient dies in the acute phase, death is often directly attributable to CVT. Most of these patients die from transtentorial herniation due to large venous infarcts.[59] In contrast, death in the chronic phase is usually caused by co-morbid conditions, especially cancer.

OUTLINE OF THE THESIS

The aim of the present thesis is to gain better insight into the epidemiology, clinical course, and outcome of CVT.

PART I   EPIDEMIOLOGY

The first part of this thesis focuses on the epidemiology of CVT. **Chapter 2** describes a cross-sectional study that investigates the incidence of CVT among hospitalized adult patients located in two provinces in The Netherlands. **Chapter 3** is a systematic review of the literature regarding the shift in sex ratio over time among patients with CVT. **Chapter 4** describes a case-control study in which we investigated the association between obesity and CVT. In **chapter 5**, we report the results of a systematic analysis of the literature on the decline in mortality over time in CVT.

PART II   CLINICAL COURSE AND OUTCOME

In the second part of this thesis, we highlight the clinical course and outcome of CVT. **Chapter 6** describes a retrospective study that reports the clinical course of adults with CVT during treatment for acute lymphoblastic leukemia. The relevance of early symptoms and treatments are explored. **Chapter 7** describes a cohort study that aimed to assess the association between hyperglycemia and clinical outcome in CVT. **Chapter 8** is a post hoc-analysis of the International Study on Cerebral Venous and dural sinus Thrombosis (ISCVT) study, in which we examined CVT associated with an infection of the head or neck. **Chapter 9** describes the frequency, pathophysiology and clinical manifestations of hydrocephalus in patients with CVT, and discusses how hydrocephalus may contribute to poor clinical outcome in these patients. **Chapter 10** describes a prospective cohort study on the efficacy of decompressive hemicraniectomy for severe cases of CVT with impending herniation. Finally, **chapter 11** summarizes the results and conclusions presented in this thesis and addresses future directions for research on CVT.

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PART I

Epidemiology

2

THE INCIDENCE OF CEREBRAL VENOUS THROMBOSIS

a cross-sectional study

Jonathan M. Coutinho, Susanna M. Zuurbier, Majid Aramideh, Jan Stam

ABSTRACT

Background
The purpose of this study was to determine the incidence of adult cerebral venous thrombosis.

Methods
A retrospective cross-sectional study was conducted among all 19 hospitals located in 2 Dutch provinces serving 3.1 million people. Adult cerebral venous thrombosis cases diagnosed between January 1, 2008, and December 31, 2010, were identified using the Dutch financial coding system for hospital care and the International Classification of Diseases, 9th Revision. Medical records of potential patients were hand searched to identify cerebral venous thrombosis cases. The Dutch National Bureau for Statistics provided population figures of the 2 provinces during 2008 to 2010.

Results
Among 9270 potential cases, we identified 147 patients diagnosed with cerebral venous thrombosis. Of these, 53 patients did not meet the inclusion criteria; therefore, 94 patients were included in the analysis. The overall incidence was 1.32 per 100.000 person-years (95% CI, 1.06-1.61). Among women between the ages of 31 and 50 years, the incidence was 2.78 (95% CI, 1.98-3.82).

Conclusions
The incidence of cerebral venous thrombosis among adults is probably higher than previously believed.

INTRODUCTION

The incidence of cerebral venous thrombosis (CVT) is estimated at 0.2 to 0.5 per 100.000 per year. [1, 2] One estimate was derived from an extrapolation of mortality and autopsy data from studies performed several decades ago.[3] Kalbag and Woolf[4] provide mortality figures from the British Registrar General. From 1952 to 1961 an average of 21.7 deaths from CVT were reported annually in a population of 56 million (0.39 deaths per million). The mortality of CVT probably varied between 20% and 50%. This gives an incidence of approximately 0.1 to 0.2 cases per 100.000. These indirectly calculated incidence rates are inaccurate, especially because improved neuroimaging has shown that, unlike previously believed, CVT often has a benign course. Other studies give estimates of 0.22[5], 0.34[6], and 1.23[7] per 100.000, but in most of these studies determination of the incidence was not the primary objective. We determined the incidence of CVT among adults in 2 provinces in The Netherlands over a 3-year period, by hand-searching the medical records of all 19 hospitals in this region.

PATIENTS AND METHODS

Study Design
We conducted a retrospective cross-sectional hospital-based population study among all 19 hospitals in the provinces of North-Holland and Flevoland. We searched for patients with CVT diagnosed between January 1, 2008, and December 31, 2010. First, we used the Dutch financial coding system for hospital care (DBC). The appropriate code for CVT is 1199, which includes infectious and non-infectious cases. Because in some instances patients might have been wrongly assigned the code 1111 "ischemic stroke" or 1102 "hemorrhagic stroke", we also compiled lists of these codes. Because we expected that the yield of CVT cases among the latter codes would be low, and the fact that CVT is rare among elderly patients, we only searched these codes for patients up to the age of 65 years. In addition, we used the International Classification of Diseases, 9th Revision, used in 10 hospitals (codes 437.6, 325, 671.5, and 437.8). This study was approved by the ethical review board of the Academic Medical Centre.

Identification of CVT Cases
We hand-searched medical records of all patients with the appropriate DBC or International Classification of Diseases, 9th Revision. Only cases confirmed by MR venography, CT venography, conventional angiography, or autopsy were included. All cerebral imaging results were reassessed by the investigators (JMC and SMZ). If the diagnosis was judged incorrect, or found to be incorrect at follow-up, the patient was excluded. We also excluded patients who lived outside the 2 provinces. Extra care was taken to avoid duplicate counts.

Statistical Analysis

We acquired the population figures of the years 2008 to 2010 from the Dutch National Bureau for Statistics. To calculate the overall incidence, we used the population of North-Holland and Flevoland aged ≥18 years as the denominator.

RESULTS

We identified 9270 potential CVT cases (Figure 1). After hand-searching all medical records, we identified 147 patients diagnosed with CVT. Fifty-three patients did not meet the eligibility criteria; therefore, 94 patients were included in the analysis. The combined adult population of the 2 provinces was 2.353.429 in 2008, 2.379.236 in 2009, and 2.405.611 in 2010. The overall annual incidence of CVT among adults was 1.32 per 100.000 person-years (95% CI, 1.06-1.61, Table 1). As expected, the incidence was significantly higher in women than men (1.86 versus 0.75) and higher among patients aged 31 to 50 (1.71).

The median age of patients was 41 years (Table 2). Fifty-two percent of female patients used oral contraceptives and 18% were pregnant or had recently given birth. The transverse and sigmoid sinuses were thrombosed most often (70% and 53%, respectively). Parenchymal lesions at baseline occurred in 44%. Nearly all patients (96%) received anticoagulant treatment. Mortality was 1% at discharge and 3% at follow-up.

TABLE 1. Incidence rates.

Population	Incidence year^{-1} 100.000^{-1}
Overall adult incidence	1.32 (1.06 – 1.61)
Subgroups	
Women	1.86 (1.44 – 2.36)
Men	0.75 (0.49 – 1.09)
Age 18-30 y	1.64 (1.05 – 2.44)
Age 31-50 y	1.71 (1.26 – 2.27)
Age >51 y	0.77 (0.48 – 1.16)
Women age 31-50 y	2.78 (1.98 – 3.82)
Men age 31-50 y	0.64 (0.29 – 1.21)

Incidence rates are given per 100.000 person-years with 95% CI in parenthesis.

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┌─────────────────────────┐
│   Patients assessed     │
│      (n = 9270)         │
└─────────────────────────┘
              │              ┌─────────────────────────┐
              │─────────────▶│        No CVT           │
              │              │       (n = 9123)        │
              ▼              └─────────────────────────┘
┌─────────────────────────┐
│ Patients diagnosed      │
│     with CVT            │
│      (n = 147)          │
└─────────────────────────┘
              │              ┌─────────────────────────────────────┐
              │              │            Excluded                 │
              │              │            (n = 53)                 │
              │─────────────▶│  – Counted twice (n = 13)           │
              │              │  – Children (n = 17)                │
              │              │  – Lived outside caption area (n = 14)│
              │              │  – Wrong diagnosis or inadequate    │
              │              │    imaging used (n = 9)             │
              ▼              └─────────────────────────────────────┘
┌─────────────────────────┐
│  Included in the study  │
│       (n = 94 )         │
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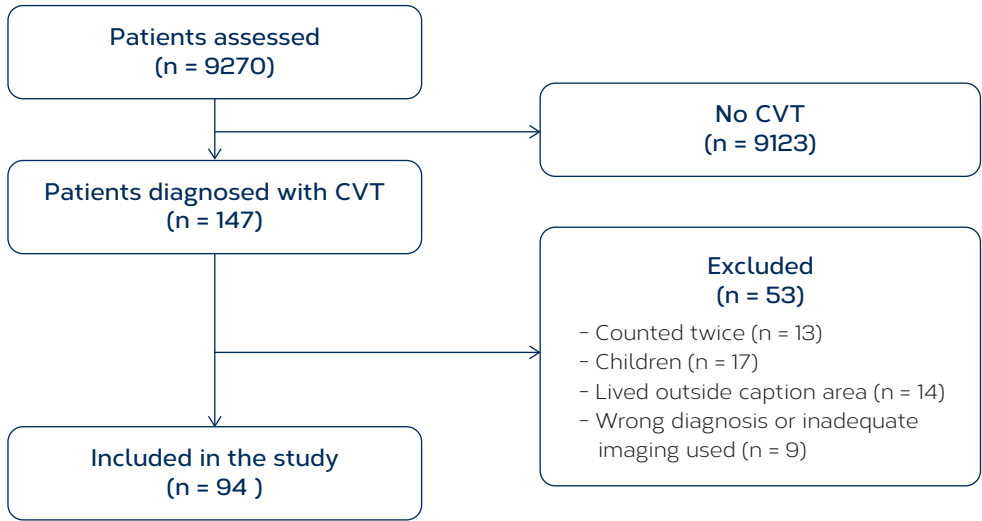
FIGURE 1. Flowchart of patient selection.

TABLE 2. Clinical and radiological manifestations.

Characteristics	
Median age, y (range)	41 (18-72)
Sex, % female	72
Oral contraceptive use, % of women	52
Pregnancy or puerperium, % of women	18
Parenchymal lesion (%)	44
Location thrombosis (%)	
Superior sagittal sinus	43
Transverse sinus	70
Sigmoid sinus	53
Straight sinus	16
Anticoagulation (%)	96
Mortality at discharge (%)	1
Mortality at follow-up (%)	3

DISCUSSION

We found an incidence of adult cerebral venous thrombosis of 1.32 per 100.000 person-years, much higher than previously published. This indicates that CVT in adults has an incidence comparable to bacterial meningitis.[8] A possible explanation is that due to an increased awareness of CVT and improved imaging techniques, CVT is more frequently diagnosed. One of the strengths of our study is that we hand-searched the medical records of almost 10.000 potential CVT cases and used strict inclusion and diagnostic criteria. Because exact figures on population distribution are available in The Netherlands, we believe that our data provide a reliable estimate of the true incidence of CVT.

Several well designed studies have examined the incidence of CVT among children. The Canadian Pediatric Ischemic Stroke Registry found an incidence of 0.67 per 100.000 per year, with a peak among neonates.[9] As a result, CVT was always believed to be more common among children than adults. In contrast, our data suggest that CVT is twice as common in adults as in children.

One previous study found an incidence similar to our study. Janghorbani et al.[7] performed a case registry in 2 hospitals in Iran and reported an incidence of 1.23 per 100.000. Their study, however, was performed in tertiary care hospitals, which may have caused referral bias. Furthermore, because recent data on population were lacking, they calculated their denominator based on an older census, which may be less accurate. Finally, it is unclear if they checked for duplicate counts or referrals from outside the caption area.

The mortality in our study, 1% at discharge and 3% at follow-up, is lower than in previous studies. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), mortality was 4% at discharge and 8% at follow-up.[10] This is in agreement with the idea that improved diagnosis has identified not only more cases, but also less severe cases with a benign course. Possibly, the almost universal application of anticoagulant treatment (96%) may have contributed to the low mortality.

Our study has several limitations. First, despite our extensive search, we cannot exclude that some cases have been missed. For instance, patients who were miscoded, who were admitted to a hospital outside the search region, or who were not treated by a neurologist would all have been missed. Thus, the incidence we found may be an underestimate of the true incidence. Another limitation is the retrospective design of our study, but because we manually checked the original medical records and imaging, we feel it is unlikely that this introduced bias.

ACKNOWLEDGEMENTS

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3

SEX DIFFERENCES IN CEREBRAL VENOUS THROMBOSIS

a systematic analysis of

a shift over time

Susanna M. Zuurbier, Saskia Middeldorp, Jan Stam, Jonathan M. Coutinho

ABSTRACT

Background

In contemporary studies, cerebral venous thrombosis is three times more common in adult women than in men. We study the change in sex ratio over time in cerebral venous thrombosis.

Methods

We systematically reviewed the literature. Any type of study with at least 40 patients with cerebral venous thrombosis that reported sex ratio was eligible. We ranked studies according to the year halfway the period of patient recruitment. Pediatric studies were analyzed separately.

Results

Out of 6068 publications identified by our search, 112 studies (23.638 patients), published between 1966 and 2014, were included. The proportion of women among patients with cerebral venous thrombosis significantly increased over time from a median of 54.8% in studies prior to 1981 to 69.8% after 2001 (p=0.002). There was a significant correlation between time of the study and proportion of women (Pearson correlation coefficient 0.25, p=0.01). Oral contraceptive use among women with cerebral venous thrombosis also increased over time (Pearson correlation coefficient 0.29, p=0.01). In contrast, the percentage of pregnancy-related cases remained stable (Pearson correlation coefficient 0.04, p=0.77). Among 1702 patients from pediatric studies, 39% were female and there was no correlation between sex ratio and time of the study (Pearson correlation coefficient –0.42, p=0.14).

Conclusions

In adult patients with cerebral venous thrombosis, there is a shift in sex ratio over time with an increase in the proportion of women, whereas this is not observed in pediatric populations. A possible explanation for this phenomenon is an increase over time in the use of oral contraceptives by adult women.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare location of venous thrombosis.[1] Risk factors for CVT partly overlap with those for deep vein thrombosis of the leg and pulmonary embolism (venous thromboembolism, VTE), such as inherited thrombophilia, pregnancy and postpartum period, use of oral contraceptives, and cancer.[2, 3] Some risk factors, such as increasing age and immobilization, are associated with VTE but not with CVT, whereas, for example, lumbar punctures and ear infections are associated with CVT but not VTE.[2-4]

In most contemporary CVT studies among adolescents and middle-aged adults, CVT is three times more common in women than men.[3] This skewed sex ratio is usually attributed to female-specific risk factors: pregnancy, puerperium, and especially oral contraceptive use.[5, 6] However, these are also recognized risk factors for VTE and in this condition the sex ratio is much more evenly distributed.[7] If oral contraceptives are indeed such an important determinant of the overrepresentation of female patients in CVT, one would expect a change in sex ratio over time that mirrors increase usage of oral contraceptives. Similarly, one would expect that among patient groups in which these female-specific risk factors are absent, i.e. children and elderly, the sex ratio would be more evenly distributed. The aim of the current study was to systematically study the change in sex ratio and female-specific risk factors over time among patients with CVT.

METHODS

Search strategy and selection criteria
We performed a systematic review of the literature. Pubmed and EMBASE databases were searched from beginning until 1 November, 2014 for publications on CVT. Relevant papers were identified from PubMed with the following search query: (sinus* [TI] AND thrombosis [TI]) OR (thrombosis [TI] AND cerebral [TI] AND (venous [TI] OR vein* [TI] OR sinus* [TI])) OR ("Sinus Thrombosis, Intracranial" [MESH]) OR (intracranial [TI] AND thrombosis [TI]). A similar query was used for EMBASE. To identify older case series, we also screened books and monographs on CVT, checked the reference lists of eligible studies, and searched the grey literature, through www.opengrey.eu. The screening process was performed independently by two of the authors (JMC and SMZ). Any disagreement was resolved by consensus or, if required, voting by a third author (JS).

To minimize bias, only studies with at least 40 patients with CVT or more were eligible. All study designs and patients of all ages were eligible, but pediatric studies were analyzed separately. Publications which did not report the sex ratio, or that selectively included women (e.g. studies on puerperal CVT), were excluded. We also

excluded redundant publications (defined as more than 50% overlap). In the case of redundant publications of the same study population, the publication with the largest study population was used. Publications written in the following languages were eligible: English, French, German, Spanish, Portuguese, and Dutch. Publications in other languages were eligible if they had an English abstract that contained sufficient information. No protocol was written for the systematic review.

Data extraction and analysis

We extracted relevant data from each study that was included in the final analysis using a predesigned case report form. Extracted data included information on study design, demographics, clinical manifestations, and reported risk factors. We ranked studies according to the year halfway the period of patient recruitment. If the authors did not report the time span of patient recruitment, we assumed a period of 10 years prior to the year of publication. The results are given as percentage of women per study and we used Pearson correlation coefficient to analyze the change in sex ratio over time.

We did various explorative subgroup analyses. We analyzed the influence of study design by stratifying into multi- versus single center studies, prospective versus retrospective studies, and large versus small sample size (dichotomized at the median number of included patients). Regarding geographical and socioeconomic factors, we stratified for origin (European versus non-European studies), income level (high or upper middle versus lower middle or low income country, according to the World Bank definition of 2014 [http://data.worldbank.org]), and birth rate of the country (low birth rate: 2.0 children per women or less)[8]. These categorizations were done based on the country of origin of the corresponding author. We also examined the change in oral contraceptive use and pregnancy among patients with CVT over time. All data were analyzed with SPSS version 20.

RESULTS

Our search returned 6068 articles (Figure 1). After screening the titles and abstracts, we selected 232 potentially eligible studies. Of these, we excluded 120 papers, mostly because of redundant data (n=54), selective inclusion of women (n=16), or no data on sex ratio (n=7); 112 studies with data from 23,638 patients, published between 1966 and 2014, fulfilled the selection criteria and were included in the analysis. Of these, 14 reported on pediatric cohorts (n=1702) and were analyzed separately.

The characteristics of the studies are shown in the Supplemental Table. In the adult studies (n=98), the median number of patients per study was 63 (interquartile range 49–113) and the median time span of patient recruitment in the studies was 10 years (range 1 to 48). One study, based on a national inpatient database, included 11.400
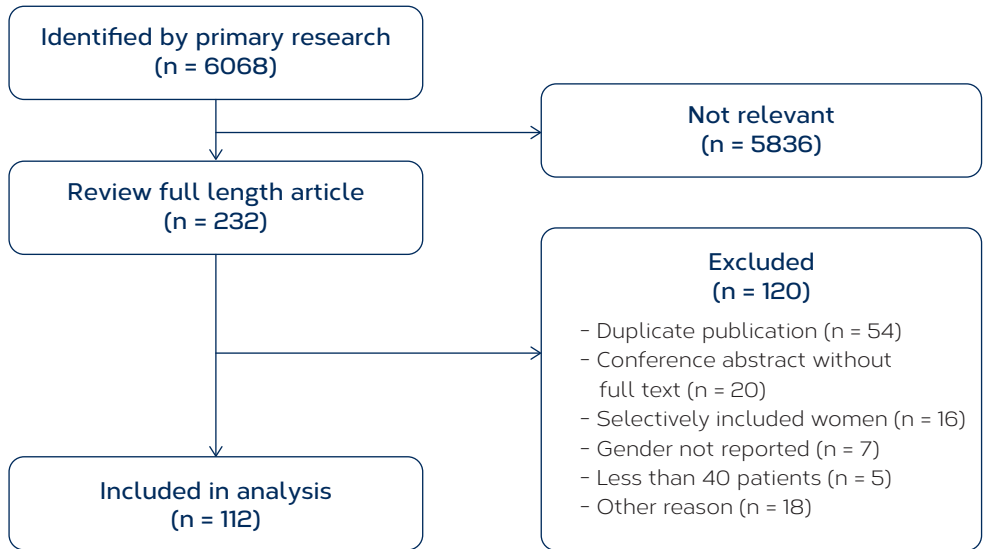
FIGURE 1. Flowchart of study selection.

patients.[9] Eleven studies (11%) did not report a time span and for these we assumed a period of 10 years prior to the year of publication. There were 19 (19%) prospective and 31 (32%) multi-center studies. In 15 studies (15%) the corresponding author came from a low or lower middle-income country. Seventy studies reported on oral contraceptive use and 73 on pregnancy and puerperium.

In adult patients, the average age was 37.0 years and overall, 65.8% were women. The most common clinical manifestations and risk factors are provided in Table 1. Overall, 38.4% of women with CVT used oral contraceptives at the time of diagnosis and 28.1% of women suffered from CVT during pregnancy or puerperium. The percentage of women per study ranged from 16% to 89%. The proportion of women significantly increased over time. In studies prior to 1981, the median percentage of women per study was 54.8%. This proportion increased to a median of 69.8% in studies after 2001 (p=0.002). There was a weak, but statistically significant correlation between time of the study and proportion of women (Pearson correlation coefficient 0.25, p=0.01, Table 2 and Figure 2A). There was one outlying study, which reported only 16% women in a cohort of patients with traumatic CVT.[10] Exclusion of this study strengthened the correlation (Pearson correlation coefficient 0.29, p=0.004). Stratification into multi- and single-center studies essentially gave the same results. Subgroup analyses by geographical and socioeconomic factors also yielded similar results as the main analysis, but the number of studies for some categories (low-income countries and countries with a high birth rate) was limited.

In European studies the correlation between time of the study and the proportion of women was stronger (Pearson correlation coefficient 0.42, p=0.005). Other subgroup analyses are presented in Table 2.

Oral contraceptive use among adult women with CVT significantly increased over time, from a median of 6.9% in studies before 1990 to a median of 46.7% in those after 2000 (correlation coefficient 0.29, p=0.01, Table 2 and Figure 2B). In contrast, the percentage of pregnancy-/puerperium related CVT cases remained stable over time (correlation coefficient 0.04, p=0.77, Table 2 and Figure 2C). In fact, in European studies, where the change in sex ratio was the most prominent, pregnancy-/puerperium related CVT cases significantly declined (correlation coefficient −0.51, p=0.003). There was no significant reduction in the proportion of infection related CVT cases (Pearson correlation coefficient −0.21, p=0.13), and traumatic CVT (Pearson correlation coefficient −0.23, p=0.11).

TABLE 1. Baseline characteristics, risk factors, and outcome.

Characteristic	n/N (%) *
Demographics	
Weighted mean age †	37.0 years
Women	15.560/23.638 (65.8)
Clinical and radiological characteristics	
Headache	5216/6603 (79.0)
Focal neurological deficit	2342/5773 (40.6)
Seizure(s)	2483/6432 (38.6)
Comatose	418/3378 (12.4)
Papilledema	1767/4930 (35.8)
Intracranial hemorrhage	1430/4179 (34.2)
Risk factors	
Oral contraceptive ‡	2013/5238 (38.4)
Pregnancy or puerperium ‡	3968/14.102 (28.1)
Infection	952/18.420 (5.2)
Malignancy	1241/18.103 (6.9)
Trauma	366/17.698 (2.1)
Outcome	
In-hospital mortality	941/ 18.388 (5.1)

Categorical variables are given as n/N, where n is the number of patients in which the variable was present and N the total number of patients for which that particular variable was reported. The percentage is given between brackets. † Recalculated from data of 58 studies, including 7197 patients. The average age was used or, if not reported, the median age. ‡ Female patients only.
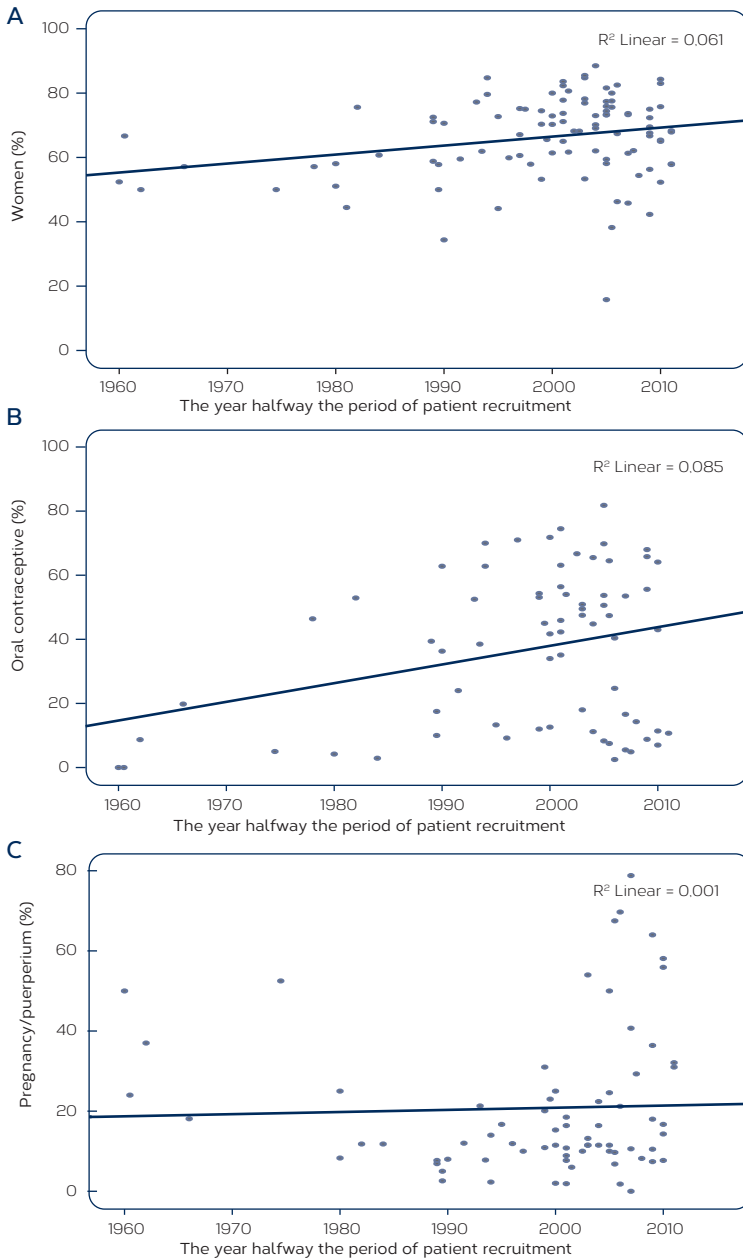
FIGURE 2.   Change in sex ratio and gender-specific risk factors. *In each figure, time is plotted on the x-axis. Studies were ranked according to the year halfway the period of patient recruitment. On the y-axis percentage of women (A), oral contraceptive use (B), and pregnancy-related CVT (C) are plotted. Each dot indicates a single study.*

TABLE 2. Change over time in sex ratio, oral contraceptive use and pregnancy related cerebral venous thrombosis.

	No. of studies	No. of patients	Correlation coefficient *	P value
Sex ratio (change in % of women)				
Adults	98	21.936	0.25	0.01
Pediatric studies	14	1702	-0.42	0.14
Subgroup analyses (adult studies only)				
Study design				
Multi-center studies	31	15.699	0.33	0.07
Single-center studies	67	6237	0.25	0.04
Prospective studies	19	2752	-0.33	0.17
Retrospective studies	79	19.184	0.32	0.005
Large sample size studies	50	19.549	0.34	0.02
Small sample size studies	48	2387	0.15	0.32
Geographical and socioeconomic factors †				
European studies	43	4528	0.42	0.005
Non-European studies	54	17.345	0.26	0.06
High-income countries	82	18.984	0.28	0.01
Low-income countries	15	2889	0.27	0.33
High birth rate	22	3449	0.40	0.07
Low birth rate	75	18.424	0.23	0.05
Other				
Studies that reported recruitment period	87	20161	0.18	0.10
Studies that reported data on oral contraceptive use	70	7731	0.36	0.003
Change in oral contraceptive use and pregnancy				
Oral contraceptives	70	7731	0.29	0.01
Pregnancy or puerperium	73	19.754	0.04	0.77

* *For each analysis, the change of the variable (sex ratio, oral contraceptive use, or pregnancy) over time is given, defined as the correlation between that variable and time of the individual studies. The change in sex ratio in pediatric studies was analyzed separately. † For one study it the country of origin was not reported and this study was excluded from these subgroup analyses.*

The 14 pediatric studies reported data on 1702 children with CVT, recruited between 1986 and 2009 (Supplemental Table). The median number of patients per study was 77 (interquartile range 53 to 156) and the median time span of the studies was 9 years (range 4 to 21). There were 5 (36%) prospective and 10 (71%) multi-center studies. Overall, 43.3% of patients were neonates (not reported in three studies). Among pediatric patients, only 39% of all cases were female (range 25 – 60%). We did not observe an increase in the proportion of females over time in pediatric studies (Pearson correlation coefficient -0.42, p=0.14, Table 2).

DISCUSSION

Our systematic review shows that the sex ratio among adult patients with CVT has shifted over time, with a gradual increase in the proportion of women. There is also an increase in the reported proportion of women with CVT that used oral contraceptives at the time of diagnosis, while the proportion of pregnancy-related CVT remained stable, and even declined in European countries.

Increased use of oral contraceptive use is one of the possible explanations for the change in sex ratio, although our study does not provide direct evidence for this hypothesis. Previous studies have shown that oral contraceptives carry an increased risk of VTE with an overall relative risk ratio of 3.5. Likewise, the risk of CVT is increased about 5-fold with the use of oral contraceptives.[11, 12] The use of modern methods of contraception by women, which includes oral contraceptives, has increased substantially since the middle of the 20th century.[13, 14] Women from developed countries use oral contraceptives more than twice as often as women from developing countries (18.4% versus 7.3%).[13] Use of oral contraceptive has become particularly popular in Western European countries, where almost half of the women aged 15-45 who are married or in a consensual relationship use oral contraceptives.[13, 15, 16] In European studies, the change in sex ratio was also the most prominent. Recent studies show that the use of oral contraceptives has stabilized in the last decade, both in developing and developed countries.[17] In our analysis of pediatric studies, we found no overrepresentation of females and no significant change in the sex ratio over time. This would suggest that in the absence of hormonal factors, the sex ratio in CVT is evenly distributed, or possibly even slightly skewed towards men. A similar observation has been reported in VTE, where the risk of a first venous thrombosis was twice as high in men compared to women without reproductive risk factors.[18]

Although increase in oral contraceptive use is a reasonable explanation for the change in sex ratio, we should consider other explanatory factors. First, the availability of MRI, which eliminated the risk of ionizing radiation, may have made it easier to diagnose CVT, especially in pregnant women. However, if this were an important

contributing factor, we would have expected to find an increase in pregnancy related CVT cases over time, which was not the case. Second, improved access to health care for women, may have increased the frequency that CVT is diagnosed in women, especially in milder cases, which are more common in women.[5, 19] Third, the proportion of septic CVT cases has decreased over time, probably due to improvement in antibiotic therapy, and this type of CVT is more common in men.[5] Finally, the studies that showed an association between oral contraceptive use and CVT, which were published in the 1990s[11, 20], may have made neurologists more aware of the possibility of CVT in young women.

One of the limitations of our systematic review is the quality of the individual studies included in the analysis. Two-thirds were single-center studies, and most were retrospective. The fact that the shift in sex ratio was of similar magnitude in the subgroup of multi-center studies would suggest that quality of study design did not have a major impact on the results. The average number of patients per study was also small. As a result of these methodological limitations, there is a substantial risk that publication bias influenced the results. We tried to limit the bias of small studies by excluding publications with less than 40 patients. Increasing this limit was not feasible, since that would have resulted in exclusion of most of the older studies. Even with a limit of 40 studies, the number of older studies was small. We also assessed the influence of bias from smaller studies by analyzing multi-center studies and studies with the largest sample size separately. In these subgroup analyses the association between time of the study and sex ratio remained statistically significant. When we included only prospective studies in the analysis, there was no association, but this might be explained by the small number of prospective studies and the fact that these were mostly performed in the past two decades. Another limitation is that the strength of the association, while statistically significant, was relatively weak. A final limitation is that we could not take into account the effect of different types of oral contraceptives on the change in sex ratio, since most studies did not report this information.

In conclusion, we found a significant change over time in the sex ratio among patients with CVT, with a gradual increase in the percentage of women. Increase use of oral contraceptives is one of the possible explanations for this phenomenon.

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SUPPLEMENTAL TABLE 1. Study characteristics of included studies.

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First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Bharatkumar[1]	2014	2003-2013 (10 yrs)#	India	R/S	185
Tufano[2]	2014	1997-2012 (15 yrs)	Italy	R/S	56
Orikaza[3]	2014	1993-2009 (16 yrs)	Brazil	P/M	72
Davoudi[4]	2014	2007-2012 (5 yrs)	Iran	P/S	94
Özen[5]	2014	2008-2010 (2 yrs)	Turkey	R/S	40
Sidhom[6]	2014	2009-2012 (3 yrs)	Tunisia	P/S	41
Geisbusch[7]	2014	1998-2013 (15 yrs)	Germany	R/S	143
De[8]	2014	2009-2012 (3 yrs)	India	R/S	476
Anadure[9]	2014	2006-2008 (2 yrs)	India	P/S	48
Coutinho[10]	2014	2000-2010 (10 yrs)	The Netherlands	R/S	53
Guner[11]	2014	2007-2013 (6 yrs)	Turkey	R/S	46
Karadas[12]	2014	2008-2011 (3 yrs)	Turkey	R/S	51
Siddiqui[13]	2014	1995-2012 (17 yrs)	US	R/M	63
Patil[14]	2014	2011-2011 (1 yrs)	India	R/S	50
Martinelli[15]	2014	2003-2013 (10 yrs)#	Italy	R/M	48
Altinkaya[16]	2014	2008-2013 (5 yrs)	Turkey	R/S	45
Korathanakhun[17]	2014	2002-2013 (11 yrs)	Tailand	R/S	90
Bon[18]	2014	2007-2013 (5 yrs)	Portugal	R/S	100
Nasr[19]	2013	2001-2008 (7 yrs)	VS	R/M	11400
Tokgoz[20]	2013	2002-2012 (10 yrs)#	Turkey	R/S	59
Aaron[21]	2013	2002-2011 (9 yrs)	India	R/S	44
Li[22]	2013	2007-2010 (3 yrs)	China	P/S	52
Pai[23]	2013	2001-2010 (9 yrs)	India	P/M	612
Bugnicourt[24]	2013	2000-2008 (8 yrs)	France	P/M	52
Jalili[25]	2013	1997-2009 (12 yrs)	Iran	R/S	62
Qu[26]	2013	2002-2007 (5 yrs)	China	R/S	62
Ekici[27]	2013	2008-2011 (3 yrs)	Turkey	R/S	52
Wolff[28]	2012	2000-2011 (11 yrs)	Portugal	R/S	45
De[29]	2012	2001-2011 (10 yrs)#	India	R/S	372
Coutinho[30]	2012	2008-2010 (2 yrs)	The Netherlands	R/M	94
Kalita[31]	2012	1995-2011 (16 yrs)	India	R/S	90
Ashjazadeh[32]	2012	2008-2010 (2 yrs)	Iran	R/S	57
Sartori[33]	2012	1998-2007 (9 yrs)	Italy	P/S	44

Pediatric study	Gender (% women)	Pregnancy/Puerperium (% women)	Oral contraceptive use (% women)
No	68	64	9
No	73	NR	54
No	78	9	56
No	83	17	64
No	75	NR	NR
No	68	32	11
No	67	2	40
No	68	NR	NR
No	46	0	17
No	77	10	82
No	52	14	11
No	84	58	7
No	73	NR	NR
No	58	31	NR
No	56	7	56
No	58	NR	NR
No	54	8	14
No	65	8	43
No	76	25	NR
No	69	NR	NR
No	61	41	NR
No	42	36	NR
No	38	7	NR
No	89	NR	NR
No	86	13	51
No	58	50	8
No	65	56	NR
No	73	NR	NR
No	73	79	6
No	72	18	68
No	53	NR	NR
No	67	11	66
No	68	10	67

First Author	Year of publication	Period of inclusion	Country lead author	Study design	Nr. of patients
Misra[34]	2012	2005-2010 (5 yrs)	India	P/S	66
Dentali[35]	2012	2001-2011 (10 yrs)#	Italy	R/M	706
Passamonti[36]	2012	1991-2010 (9 yrs)	Italy	R/S	152
Narayan[37]	2012	2002-2010 (8 yrs)	India	P/S	428
Hinnell[38]	2012	1999-2009 (10 yrs)	Canada	R/S	108
Chiquete[39]	2012	2010-2010 (1 yr)	Mexico	R/M	194
Ruiz[40]	2012	2002-2004 (2 yrs)	Mexico	P/M	59
Kumral[41]	2012	1998-2010 (12 yrs)	Turkey	R/S	220
Algahtani[42]	2011	1990-2010 (20 yrs)	Saudi Arabia	R/M	111
Ashjazadeh[43]	2011	2000-2008 (8 yrs)	Iran	R/S	124
Bugnicourt[44]	2011	2002-2007 (5 yrs)	France	P/S	43
Vembu[45]	2011	2000-2010 (10 yrs)	Kuwait	R/S	71
Cesarman[46]	2011	2000-2010 (10 yrs)#	Mexico	P/ S	40
Santos[47]	2011	2004-2007 (3 yrs)	Portugal	R/S	49
Halesha[48]	2011	2005-2006 (1 yr)	India	R/S	50
Sanz[49]	2011	1995-2007 (12 yrs)	Spain	R/S	52
Moharir[50]	2011	1992-2009 (17 yrs)	Canada	P/S	104
Tuckuviene[51]	2011	1994-2006 (12 yrs)	Denmark	R/M	40
Nowak[52]	2011	2002-2009 (7 yrs)	Germany	R/S	154
Martinelli[53]	2010	1992-2008 (16 yrs)	Italy	R/M	107
Sahraian[54]	2010	2003-2008 (5 yrs)	Iran	P/M	41
Putaala[55]	2010	1990-2008 (18 yrs)	Finland	R/S	91
Almandoz[56]	2010	2000-2009 (9 yrs)	US	R/S	57
Rizzo[57]	2010	1996-2006 (10 yrs)	Italy	R/S	40
Moharir[58]	2010	1995-2005 (10 yrs)#	Canada	P/S	162
Grunt[59]	2010	2000-2008 (8 yrs)	Switzerland	P/M	65
Jordan[60]	2010	2003-2007 (4 yrs)	VS	R/M	84
Berfelo[61]	2010	1999-2009 (10 yrs)	Netherlands	R/M	52
Vieira[62]	2010	2001- 2007 (6 yrs)	Portugal	R/M	53
English[63]	2009	1995-2004 (9 yrs)	US	R/S	61
Koopman[64]	2009	1994-2008 (14 yrs)	The Netherlands	R/S	79
Yesilot[65]	2009	1984-2006 (22 yrs)	Turkey	R/S	68
Saadoun[66]	2009	1974-2006 (32 yrs)	France	R/S	64
Damak[67]	2009	1997-2006 (9 yrs)	France	P/S	62
Normann[68]	2009	2004-2009 (5 yrs)	Germany	R/S	52
Golomb[69]	2009	2003-2007 (4 yrs)	VS	R/M	262

Pediatric study	Gender (% women)	Pregnancy/Puerperium (% women)	Oral contraceptive use (% women)
No	62	29	5
No	74	11	54
No	74	11	75
No	46	21	25
No	62	16	45
No	76	NR	NR
No	85	54	18
No	69	22	11
No	70	15	13
No	70	12	66
No	74	NR	NR
No	59	NR	70
No	83	70	3
No	78	NR	47
No	80	68	8
No	71	2	35
Yes	28	–	–
Yes	58	–	–
Yes	47	–	–
No	73	12	72
No	76	10	65
No	70	11	53
No	16	NR	NR
No	65	8	42
Yes	34	–	–
Yes	32	–	–
Yes	26	–	–
Yes	25	–	–
Yes	43	–	–
No	66	23	45
No	82	19	63
No	44	17	13
No	34	NR	36
No	81	6	54
Yes	40	–	–
Yes	35	–	–

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First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Khealani[70]	2008	1991–2007 (16 yrs)	Pakistan	R/M	109
Xavier[71]	2008	1998–2006 (8 yrs)	Brazil	R/M	44
Bellucci[72]	2008	2003–2007 (4 yrs)	France	R/S	87
Wasay[73]	2008	1991–2001 (10 yrs)	US	R/M	182
Wysokinska[74]	2008	1995–2005 (10 yrs)	US	R/S	163
Reuner[75]	2008	1997–2007 (10 yrs)[#]	Germany	R/M	78
Nwosu[76]	2008	1986–2007 (21 yrs)	VS	R/ S	59
Wasay[77]	2008	1992–2001 (9 yrs)	Pakistan	R/S	70
Fernandez[78]	2007	1990–2005 (15 yrs)	Spain	R/S	126
Stolz[79]	2007	2000–2005 (5 yrs)	Germany	P/M	121
De Stefano[80]	2007	1994–2006 (12 yrs)	Italy	R/S	45
Kenet[81]	2007	1996–2005 (9 yrs)	Israel	R/M	396
Gosk[82]	2006	1978–2001 (23 yrs)	US	R/S	154
Masuhr[83]	2006	1976–2004 (28 yrs)	Germany	P/M	194
Anand[84]*	2006	1995–1999 (4 yrs)	India	R/S	99
Anand[84]*	2006	2000–2003 (3 yrs)	India	R/S	180
Maqueda[85]	2006	1985–2002 (17 yrs)	Belgium	R/S	54
Crassard[86]	2005	1999–2003 (4 yrs)	France	R/S	73
Stolz[87]	2005	1985–2001 (16 yrs)	Germany	R/S	79
Ferro[88]	2004	1998–2001 (3 yrs)	Portugal	P/M	624
Martinelli[89]	2003	1991–2002 (11 yrs)	Italy	R/S	121
Bergui[90]	2003	1993–2002 (9 yrs)	Italy	R/S	48
Mehraein[91]	2003	1992–2002 (10 yrs)[#]	Germany	R/S	79
Heller[92]	2003	1995–2002 (7 yrs)	Germany	P/M	149
Wasay[93]	2001	1981–1997 (16 yrs)	US	R/M	40
Ferro[94]	2001	1980–1998 (18 yrs)	Portugal	R/M	142
Saw[95]	1999	1986–1997 (11 yrs)	Australia	R/S	42
de Bruijn[96]	1999	1992–1996 (4 yrs)	The Netherlands	P/M	59
Ludemann[97]	1998	1992–1997 (5 yrs)	Germany	R/M	55
Brucker[98]	1998	1991–1996 (5 yrs)	Germany	R/M	42
Reune [99]	1998	1967–1997 (30 yrs)	Germany	R/M	45
Daif[100]	1995	1985–1994 (9 yrs)	Saudi Arabia	R/M	40
Bienfait[101]	1995	1970–1990 (20 yrs)	The Netherlands	R/M	62
Dormont[102]	1994	1984–1994 (10 yrs)[#]	France	R//M	53
Diaz[103]	1992	1942–1990 (48 yrs)	US	R/M	203
Karabudak[104]	1990	1979–1989 (10 yrs)	Turkey	R/S	56

Pediatric study	Gender (% women)	Pregnancy/Puerperium (% women)	Oral contraceptive use (% women)
No	53	31	12
No	68	NR	NR
No	82	12	51
No	60	12	9
No	61	2	34
No	78	12	48
Yes	39	–	–
Yes	60	–	–
No	58	NR	NR
No	77	12	50
No	80	25	42
Yes	40	–	–
No	58	3	18
No	71	8	63
No	61	NR	NR
No	62	NR	NR
No	80	2	63
No	84	16	46
No	77	21	53
No	75	20	54
No	75	10	71
No	75	NR	NR
No	67	NR	NR
Yes	44	–	–
No	73	7	NR
No	71	8	39
No	60	12	24
No	85	14	70
No	73	NR	NR
No	62	8	39
No	76	12	53
No	50	5	10
No	58	8	NR
No	59	NR	NR
No	57	18	20
No	61	12	3

First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Samuel[105]	1987	1978-1984 (6 yrs)	South Africa	R/S	45
Gates[106]	1986	1975-1985 (10 yrs)	Australia	R/M	47
Rousseaux[107]	1985	1973-1983 (10 yrs)	France	R/S	49
Nagpal[108]	1983	1967-1982 (15 yrs)	India	R/S	80
Huhn[109]	1971	1951-1970 (19 yrs)	Germany	R/S	120
Krayenbuhl[110]	1968	1957-1967 (10 yrs)[#]	Switzerland	R/S	92
Weber[111]	1966	1955-1965 (10 yrs)[#]	Unknown	R/S	63

This study describes 2 different time spans of patient inclusion. [#] Because these studies did not report the period of inclusion, a time span of 10 years was assumed. P indicates prospective; R, retrospective; M, multi-center; S, single-center; NR, not reported.

Pediatric study	Gender (% women)	Pregnancy/Puerperium (% women)	Oral contraceptive use (% women)
No	44	NR	NR
No	51	25	4
No	57	NR	46
No	50	53	5
No	67	24	0
No	50	37	9
No	52	50	0

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4

THE RISK OF CEREBRAL VENOUS THROMBOSIS IN OBESE WOMEN

Susanna M. Zuurbier*, Marcel Arnold*, Saskia Middeldorp, Anne Broeg-Morvay
Suzanne M. Silvis, Mirjam R. Heldner, Julia Meisterernst, Banne Nemeth
Eva R. Meulendijks, Jan Stam, Suzanne C. Cannegieter, Jonathan M. Coutinho
*Contributed equally

ABSTRACT

Background

Obesity is a risk factor for deep vein thrombosis of the leg and pulmonary embolism. To date, however, whether obesity is associated with adult cerebral venous thrombosis (CVT) has not been assessed. The objective was to assess whether obesity is a risk factor for CVT.

Methods

A case-control study was performed in consecutive adult patients with CVT admitted from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December 31, 2014, to the Academic Medical Center in Amsterdam, the Netherlands, or Inselspital University Hospital in Berne, Switzerland. The control group was composed of individuals from the control population of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis), which was a large Dutch case-control study performed from March 1, 1999, to September 31, 2004, and in which risk factors for deep vein thrombosis and pulmonary embolism were assessed. Data analysis was performed from January 2 to July 12, 2015. Obesity was determined by body mass index (BMI). A BMI of 30 or greater was considered to indicate obesity, and a BMI of 25 to 29.99 was considered to indicate overweight. A multiple imputation procedure was used for missing data. We adjusted for sex, age, history of cancer, ethnicity, smoking status, and oral contraceptive use. Individuals with normal weight (BMI <25) were the reference category.

Results

The study included 186 cases and 6134 controls. Cases were younger (median age, 40 versus 48 years), more often female (133 [71.5%] versus 3220 [52.5%]), more often used oral contraceptives (97 [72.9%] versus 758 {23.5%] of women), and more frequently had a history of cancer (17 [9.1%] versus 235 [3.8%]) compared with controls. Obesity (BMI >30 kg/m^2) was associated with an increased risk of CVT (adjusted odds ratio [OR], 2.63; 95% confidence interval [CI], 1.53-4.54). Stratification by sex revealed a strong association between CVT and obesity in women (adjusted OR, 3.50; 95% CI, 2.00-6.14) but not in men (adjusted OR, 1.16; 95% CI, 0.25-5.30). Further stratification revealed that, in women who used oral contraceptives, overweight and obesity were associated with an increased risk of CVT in a dose-dependent manner (BMI 25-29.9: adjusted OR, 11.87; 95% CI, 5.94-23.74; BMI >30: adjusted OR, 29.26; 95% CI, 13.47-63.60). No association was found in women who did not use oral contraceptives.

Conclusions

Obesity is a strong risk factor for CVT in women who use oral contraceptives.

INTRODUCTION

Various studies[1-6] have identified obesity as a risk factor for deep vein thrombosis of the leg and pulmonary embolism, collectively called venous thromboembolism (VTE). A body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30 or more increases the risk of VTE approximately 2-fold compared to a normal BMI (<25), and this risk increases more with higher BMIs. Individuals with a BMI greater than 40 have an approximately 3 times higher risk.

Cerebral venous thrombosis (CVT) is a rare thrombotic condition that mainly affects young adults and children.[7] Risk factors for CVT partly overlap with those for VTE and include thrombophilia, cancer, and oral contraceptive use.[8, 9] Other risk factors, such as local infections and head trauma, are specific for CVT.[10] Some diseases, such as acute lymphoblastic leukemia, are associated with CVT and VTE, but the association is stronger for CVT.[11]

To our knowledge, whether obesity is associated with adult CVT has not been assessed. One study[12] found that obesity is more common in children with CVT (55%) compared with controls (32%), but the sample size was small (22 cases). In addition, this study[12] used historical controls and did not adjust for confounding variables. Moreover, because the clinical presentation and risk factors of CVT are different for children and adults,[13] this result cannot be generalized to adult patients. In the current study, we examined whether obesity is a risk factor for adult CVT.

METHODS

Study design and patient selection

We performed an unmatched case-control study. The controls were recruited from March 1, 1999, through September 31, 2004, and the cases were recruited from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December 31, 2014. Data analysis was performed from January 2 to July 12, 2015.

Cases were patients with CVT included in 2 prospective cohorts from the Academic Medical Center in Amsterdam, the Netherlands, and Inselspital University Hospital in Berne, Switzerland. In these hospitals, data on consecutive adult patients with CVT have been recorded since July 2006 (Amsterdam) and October 2009 (Berne). We included patients who were admitted until December 2014. The diagnosis of CVT was confirmed with computed tomography venography, magnetic resonance venography, angiography, or autopsy in all patients in accordance with international guidelines.[14]

Controls were healthy individuals who participated in the Dutch Multiple Environ-mental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study.

The MEGA study is a case-control study performed in the Netherlands that included 4956 consecutive patients aged 18–70 with a first deep vein thrombosis of the leg or pulmonary embolism from March 1, 1999, through September 31, 2004. Details of this study have been reported.[15] Partners of patients and individuals identified by random digit dialing were asked to participate as controls. In total, 6297 controls (3297 partners and 3000 random digit dialing) were included. These participants were between the ages of 18 and 70 years and had no history of venous thrombosis. We excluded women (cases and controls) who were pregnant or had given birth less than 12 weeks earlier.

The Medical Ethics Committee Academic Medical Center, Committee Medical Ethics Leiden University Medical Centre, and Cantonal Ethics Commission Bern approved the study. Written informed consent was obtained from all participants included in the MEGA study and the Berne cohort. For the patients with CVT included in the Amsterdam cohort, written informed consent was not required under Dutch law because only observational data were collected.

Data collection and definition of obesity
Baseline characteristics, risk factors for thrombosis, imaging findings, and clinical outcome were recorded using a standardized case report form for cases. Each control completed a detailed questionnaire on acquired risk factors for thrombosis, which included self-reported current height and weight. In accordance with the definitions of the World Health Organization, BMI was categorized as follows: normal weight, BMI less than 25; overweight BMI of 25 to 29.99; and obesity, BMI of 30 or greater.

Statistical Analysis
A multiple imputation procedure was used for missing data on height, weight, oral contraceptives use, smoking status, history of cancer, and ethnicity.[16] In total, 5 datasets were imputed, and results were pooled according to Rubin's rules. We applied multivariate logistic regression analysis to study the association between obesity and CVT. Individuals with a normal BMI (<25) were the reference category. In a separate analysis, we included BMI as a continuous variable in the model. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated. We adjusted for the following prespecified variables: sex, age (as a continuous variable), history of cancer, ethnicity, smoking status, and oral contraceptive use. On the basis of a previous report,[4] we performed predefined subgroup analyses in which we studied the influence of sex and oral contraceptive use on the association between obesity and CVT. $p<0.05$ was considered statistically significant. All data were analyzed with SPSS statistical software, version 20 (SPSS Inc).

RESULTS

There were 192 cases and 6297 controls within the specified period. We excluded 6 cases and 163 controls because of pregnancy or recent delivery; therefore, the study population consisted of 186 cases and 6134 controls. The numbers of patients for whom data were missing were as follows: weight, 539 (57 cases and 482 controls); height, 547 (64 cases and 483 controls); oral contraceptive use, 32 (6 cases and 26 controls); history of cancer, 20 (1 case and 19 controls); smoking status, 487 (57 cases and 430 controls); and ethnicity, 423 (38 cases and 385 controls). In total, BMI could not be calculated without imputation in 69 cases because height or weight was not available. Eleven of these cases (15.9%) had obesity listed in their medical history.

Cases were younger (median age, 40 versus 48 years), more often female (133 [71.5%] versus 3220 [52.5%]), more often used oral contraceptives (97 [72.9%] versus 758 [23.5%] women), and more frequently had a history of cancer (17 [9.1%] versus 235 [3.8%]), compared with controls (Table 1). The most common clinical manifestations of patients with CVT are provided in Table 2.

Mean BMI was higher in cases than controls (26.7 versus 25.6, p=0.01). After adjustment for confounding variables, the risk of CVT was increased in patients with obesity (BMI ≥30; adjusted OR, 2.63; 95% CI, 1.53–4.54) compared with patients with a normal BMI (Table 3). Overweight (BMI 25.0–29.99) was not associated with CVT (adjusted OR, 1.37; 95% CI, 0.80–2.36). When included as a continuous variable, BMI was also associated with an increased risk of CVT (adjusted OR per 1-unit increase in BMI, 1.09; 95% CI, 1.05–1.13, p<0.001).

Stratification by sex revealed no statistically significant association between obesity and the risk of CVT in men (adjusted OR, 1.16; 95% CI, 0.25–5.30, Table 4). In women, overweight and obesity were associated with CVT (BMI 25–29.9; adjusted OR, 1.71; 95% CI, 1.01–2.91; BMI ≥30 adjusted OR, 3.50; 95% CI, 2.00–6.14).

We also stratified for oral contraceptive use (Table 5). Among women who did not use oral contraceptives, we found no association between obesity and CVT (BMI ≥30; adjusted OR, 1.29; 95% CI, 0.46–3.66). In contrast, in women who used oral contraceptives, obesity was strongly associated with the risk of CVT. Compared with women with a normal weight who did not use oral contraceptives, obese women taking oral contraceptives had a 29-fold increased risk of CVT (adjusted OR, 29.26; 95% CI, 13.47–63.60). The risk of CVT was also increased in overweight women who used oral contraceptives (BMI 25–29.99: adjusted OR, 11.87; 95% CI, 5.94–23.74).

TABLE 1. Baseline characteristics.

Characteristics	Cases (n=186)	Controls (n=6134)
Age, median (IQR), y	40 (28-49)	48 (38-57)
Female sex	133/186 (71.5)	3220/6134 (52.5)
Oral contraceptive use *	97/133 (72.9)	758/3220 (23.5)
History of cancer	17/186 (9.1)	235/6134 (3.8)
White ethnicity	167/186 (89.8)	5805/6134 (94.6)
Current smoker	36/186 (19.4)	1980/6134 (32.3)

*Data are presented as number/total number (percentage) of study participants unless otherwise indicated. The number of events was divided by the total number (unknown/missing cases excluded) to calculate the percentage. * in women only. IQR indicates inter quartile range.*

TABLE 2. Baseline characteristics of cerebral venous thrombosis cases.

Characteristics	No. / Total No. (%) of Cases (n=186) *
Headache	163/182 (89.6)
Focal neurological deficits	115/182 (63.2)
Seizures	79/184 (52.0)
Papilledema	38/148 (25.7)
Hemorrhagic infarcts or intracerebral hemorrhage	76/182 (41.8)
Cerebral edema or infarction without hemorrhage	39/182 (21.4)

* The number of cases was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

TABLE 3. Association between obesity and cerebral venous thrombosis.

	No. (%) of Study Participants *		OR (95% CI)	
BMI	Cases (n=186)	Controls (n=6134)	Unadjusted	Adjusted †
<25	85 (45.7)	3025 (49.3)	1 [Reference]	1 [Reference]
25-29.99	59 (31.7)	2299 (37.5)	0.93 (0.57-1.50)	1.37 (0.80-2.36)
≥30	42 (22.6)	810 (13.2)	1.85 (1.14-3.00)	2.63 (1.53-4.54)

* The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate proportion. † The multivariate model is adjusted for sex, age, history of cancer, ethnicity, smoking status, and oral contraceptive use. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio; CI, confidence interval.

TABLE 4. Stratification by sex.

| BMI | No. (%) of Study Participants * | | OR (95% CI) | |
	Cases (n= 53 Men and 133 Women)	Controls (n= 2914 Men and 3220 Women	Unadjusted	Adjusted †
Men				
<25	27 (50.9)	1277 (43.8)	1 [Reference] ‡	1 [Reference] ‡
25-29.99	18 (34.0)	1270 (43.6)	0.66 (0.30-1.45)	0.80 (0.35-1.80)
≥30	8 (15.1)	367 (12.6)	1.04 (0.26-4.17)	1.16 (0.25-5.30)
Women				
<25	57 (42.9)	1748 (54.3)	1 [Reference] ‡	1 [Reference] ‡
25-29.99	42 (31.6)	1028 (31.9)	1.24 (0.75-2.05)	1.71 (1.01-2.91)
≥30	34 (25.6)	444 (13.8)	2.30 (1.39-3.81)	3.50 (2.00-6.14)

* The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate percentage. † The multivariate model is adjusted for age, history of cancer, ethnicity, and smoking status. In the subgroup analysis for women, we also adjusted for oral contraceptive use. ‡ Patients with a BMI less than 25 were the reference category. BMI indicates Body Mass Index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio; CI, confidence interval.

TABLE 5. Stratification by oral contraceptive use in women.

| BMI | No. (%) of Study Participants * | | |
	Cases (n=129)	Controls (n=3148)	Adjusted OR (95% CI) †
No OC use			
<25	17 (13.2)	1190 (37.8)	1 ‡
25-29.99	11 (8.5)	843 (26.8)	0.85 (0.30-2.41)
≥30	7 (5.4)	384 (3.1)	1.29 (0.46-3.66)
OC use			
<25	36 (27.9)	486 (15.4)	5.09 (2.58-10.02)
25-29.99	31 (24.0)	186 (5.9)	11.87 (5.94-23.74)
≥30	27 (20.9)	59 (1.9)	29.26 (13.47-63.60)

* The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate the percentage. † The multivariate model is adjusted for age, history of cancer, ethnicity, and smoking status. ‡ Patients with a BMI less than 25 without OC use were the reference category. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); OC, oral contraceptive; OR, odds ratio; CI, confidence interval.

DISCUSSION

Our study indicates that obesity (BMI ≥30) is associated with an increased risk of CVT. This association appears to be fully attributable to a strongly increased risk in women who use oral contraceptives. Among these women, obesity was associated with an almost 30-fold increased risk of CVT compared with women of normal weight who did not use oral contraceptives. In men and women who do not use oral contraceptives, we found no association between CVT and obesity.

In VTE, the association with obesity is also stronger in women than men. In a large cohort study,[5] a BMI in the highest quartile increased the risk of VTE 2.8-fold for women and 1.7-fold for men. Another study[3] confirmed similar effect sizes. Only a few studies[4, 17, 18] have examined the interaction between oral contraceptive use and obesity on the risk of VTE. Pomp et al[4] found an odds ratio of 24 among women with a BMI of 30 or greater who used oral contraceptives compared with non-users of oral contraceptives who were of normal weight. In another study,[17] the risk of VTE in oral contraceptive users with a BMI of 30 or greater was increased approximately 10-fold. A possible interaction between oral contraceptives and obesity has also been observed in ischemic stroke. In a case-control study by Kemmeren et al,[18] the risk of ischemic stroke in women who used oral contraceptives was approximately doubled in those with obesity.

Among oral contraceptive users, the risk of CVT was higher in those with obesity (BMI ≥30) than in women who were overweight (BMI 25-29.99). This dose-response effect, in combination with the magnitude of the effect size and the evidence that obesity is also associated with VTE[2, 4, 19], favors a causal association among obesity, oral contraceptive use, and CVT.[20] One mechanism by which obesity could increase the risk of thrombosis are changes in coagulation factor levels. Compared with women with a normal weight, obese women have higher plasma concentrations of prothrombotic factors, such as plasminogen activator inhibitor 1 and von Willebrand factor.[21] Obesity is also associated with increased activated protein C resistance and higher concentrations of factor VIII, which are risk factors for thrombosis.[22] Use of oral contraceptives also leads to increased activated protein C resistance,[23] which might explain the synergistic effect of both risk factors that we observed.

It is important to determine whether the control group we used is representative of the healthy population. In our study, the prevalence of a BMI of 30 or greater was 12.6% and 13.8% among male and female controls, respectively. These percentages are similar to the findings of a study[24] among healthy adults from the Netherlands that was performed in the same period as the MEGA study. The prevalence of a BMI above 25 among men and women is also comparable to the results of that study.

Of interest, obesity is also a risk factor for idiopathic intracranial hypertension (IIH). Patients with IIH most often present with headache, papilledema, and decreased visual acuity. Identical symptoms occur in intracranial hypertension owing to impaired venous return in patients with chronic CVT.[25] Before the introduction of computed tomography and magnetic resonance venography, it was not uncommon for patients with CVT to be misdiagnosed as having IIH.[26, 27] Like CVT, IIH is far more common in women than in men, and the association between IIH and obesity is also stronger in women than men.[28-30] Given these resemblances, it is intriguing to speculate on a possible common pathogenesis by which obesity increases the risk of both conditions in women. It has been hypothesized that IIH is caused by decreased outflow from the cerebral venous system, possibly owing to stenosis of the transverse sinuses or insufficiency of the valves in the jugular veins.[31, 32] Studies[31, 33] have suggested that obesity enhances this mechanism by transmittance of increased intra-abdominal pressure to the cerebral venous system. On the other hand, there are also data indicating that the sinus stenosis seen in IIH is secondary to the increased intracranial pressure, and is reversible after removal of cerebrospinal fluid.[34] The effect of stenting of the cerebral sinuses has been examined in patients with IIH but only in small and uncontrolled series, and the data are inconclusive.[35,36] Prospective studies[37, 38] evaluating the efficacy of cerebral venous sinus stenting in IIH are currently ongoing.

Our study has several limitations. First, we could include only a relatively small number of patients with CVT, especially men, and women without oral contraceptive use. We cannot exclude that the absent association between obesity and CVT in these groups is the result of this limited sample size. Second, we were unable to examine whether genetic thrombophilia influences the association between obesity and CVT, because screening for thrombophilia was not performed in most cases. Thrombophilia should be the focus of a future study given that there is a synergistic effect between oral contraceptives and thrombophilia on the risk of CVT[9, 39] and between obesity and thrombophilia on the risk of VTE.[4] Third, data on the key variables height and weight were missing in a substantial proportion of cases because these measurements were not recorded in all patients. This lack of data on height and weight could have underpowered the study and biased the results if the reason the data were missing was not random. To minimize this potential bias, we used a multiple imputation procedure.[16, 40] The fact that 15.9% of cases in which no BMI could be calculated had obesity listed in their medical history also suggest that obesity was not infrequent among cases with missing BMI. Fourth, instead of measuring height and weight, we used self-reported data to calculate BMI, which could be less accurate, although a previous study[6] found an excellent correlation between self-reported and measured BMI. Moreover, because measurements were self-reported for cases and controls, any inaccuracy would be expected to affect both groups, which would decrease the risk of bias. Fifth, there was a time difference in recruitment between cases and controls. The controls were recruited from March

1, 1999, through September 31, 2004, whereas the cases were recruited from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December,31, 2014. A change in prevalence of obesity in that period could theoretically have biased the results. However, the time difference seems to be too small to explain the results and would also not explain why we only observed an association in women who used oral contraceptives. Finally, we cannot exclude the possibility that residual confounding influenced the results. Some variables, such as obstructive sleep apnea syndrome, were not available for controls. Obstructive sleep apnea syndrome is a risk factor for both obesity and VTE, although, to our knowledge, an association with CVT has never been reported.[41, 42]

The increased risk of VTE and CVT associated with oral contraceptives in the presence of obesity might make physicians reluctant to prescribe oral contraceptives to obese women. However, although the relative risks are increased substantially, the absolute risks of CVT are still small.[43] Moreover, withholding oral contraceptives may lead to an increase in unintended pregnancies and thus the number of pregnancy-related thrombosis cases.[44] Nevertheless, obese women should be informed about the increased risk of thrombosis if they use oral contraceptives, especially if other risk factors are present. Alternative methods of contraception that are not associated with thrombosis, such as an intra-uterine device, might be offered to these women.

CONCLUSIONS

To our knowledge, this is the first case-control study that examined the association between obesity and CVT. Our results suggest that obesity is associated with a substantially increased risk of CVT in women who use oral contraceptives. This increased risk should be taken into consideration when prescribing oral contraceptives to obese women.

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5

DECLINING MORTALITY IN CEREBRAL VENOUS THROMBOSIS

a systematic review

Jonathan M. Coutinho, Susanna M. Zuurbier, Jan Stam

ABSTRACT

Background

Cerebral venous thrombosis (CVT) is nowadays considered a disease with a good outcome in most cases, but in the past, these patients were believed to have a grave prognosis. We systematically studied the apparent decline in mortality of patients with CVT over time.

Methods

A systematic review of the literature (MEDLINE and EMBASE) was performed. Studies with ≥40 patients with CVT that reported mortality at discharge or follow-up were eligible. Duplicate publications based on the same patient cohort were excluded. Studies were ranked according to the year halfway the period of patient inclusion. Two of the authors independently screened all eligible studies.

Results

We screened 4585 potentially eligible studies, of which 74 fulfilled the selection criteria. The number of patients per study varied from 40 to 706 (median, 76). Data from 8829 patients with CVT, included from 1942 to 2012, were analyzed. The average age was 32.9 years, and 64.7% were women. There was a significant inverse correlation between mortality and year of patient recruitment (Pearson correlation coefficient, −0.72; $p<0.001$). In a sensitivity analysis, the correlation remained significant after exclusion of studies published before 1990, retrospective studies, or single-center studies. Both the frequency of focal neurological deficits and coma also decreased significantly over time (correlation coefficient, −0.50 and −0.52).

Conclusions

There is a clear trend in declining mortality among patients with CVT over time. Possible explanations are improvements in treatment, a shift in risk factors, and, most importantly, the identification of less severe cases by improved diagnostic methods.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare type of stroke that mainly affects young adults and children.[1-3] In the past, CVT was thought to carry a poor prognosis and the majority of patients did not survive.[4] In recent studies, however, the prognosis seems to be much more favorable. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), mortality at discharge was only 4.3%.[5] A multi-center study from Pakistan found a similar mortality of 5%.[6] We performed a systematic review of the literature to examine the apparent decline in mortality of CVT over time and to identify possible causes.

METHODS

Search strategy
We searched MEDLINE and EMBASE databases for publications on CVT up until April 1, 2013, using the following search term: (sinus* [TI] AND thrombosis [TI]) OR (thrombosis [TI] AND cerebral [TI] AND (venous [TI] OR vein* [TI] OR sinus* [TI])) OR (˝Sinus Thrombosis, Intracranial˝[MESH]) OR (intracranial [TI] AND thrombosis [TI]). To identify older case series, we also screened books and monographs on CVT. Furthermore, we cross-checked the reference lists of eligible studies to find additional studies. The entire screening process was performed independently by 2 of the authors (JMC and SMZ). If there was no consensus, the third author (JS) made the final decision to include or exclude a study.

Study selection
Studies were eligible if they reported ≥40 patients with CVT and provided mortality data at discharge or follow-up for ≥80% of patients. Only studies with original data were included. Both adult and pediatric (including neonatal) series were eligible. We took care to exclude duplicate publications based on the same patient cohort (>50% overlap). Patient cohorts with a selection bias towards mortality (autopsy series) or survival (e.g., studies on long-term complications) were excluded. We also excluded studies based on national hospital population databases because of lack of verification of the source data. Publications written in the following languages were eligible: English, French, German, Spanish, Portuguese, and Dutch. Publications in other languages were eligible if they had an English abstract that contained sufficient data. We initially screened the title and abstract of all articles identified by the primary search. Publications that were potentially eligible were analyzed in full detail.

Statistical analysis
We extracted data on study design, demographics, baseline clinical manifestations, risk factors, ancillary investigations, treatment, and outcome from all eligible publications. Studies in which less than one third of patients were treated with heparin

were scored as no heparin. Studies were ranked according to the year halfway the period of patient inclusion. If no time span was reported, we assumed a period of inclusion of 10 years before the year of publication. Based on the country of origin of the corresponding author, we classified studies as coming from high- (high or upper middle) or low- (lower middle or low) income countries, using the definition of the World Bank (http://data.worldbank.org). We used Pearson correlation to analyze trends in mortality over time. We used the mortality at discharge, or, if this was not reported, the mortality at follow-up. Sensitivity analyses on change in mortality over time were performed including only prospective studies, multi-center studies, studies published after 1990, studies from high-income countries, and studies with only adult patients. To identify potential explanatory factors for the decline in mortality, we analyzed the change in frequency over time of the following variables: age, coma, focal neurological deficits, seizures, intracerebral hemorrhage, infection-related CVT, malignancy-related CVT, traumatic CVT and oral contraceptive us. All data were analyzed with SPSS, version 20.
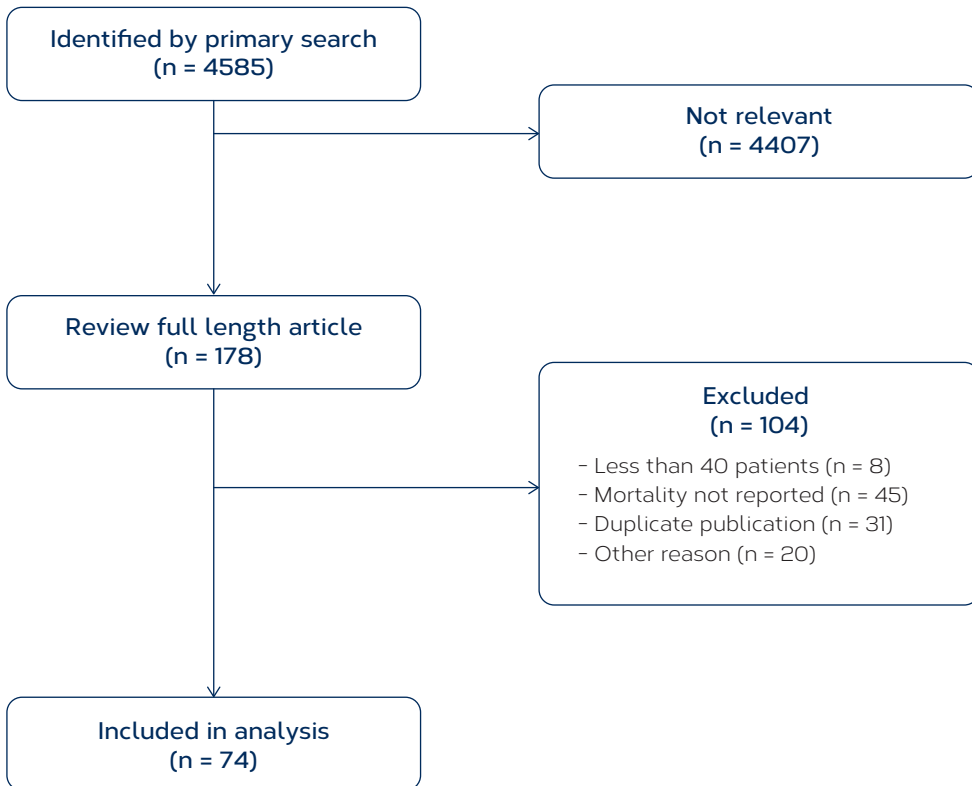

FIGURE 1. Flowchart of study selection.

TABLE 1. Baseline Characteristics, Risk factors and Treatment.

Characteristic	n/N (%) *
Demographics	
Age, y, mean †	32.9 years
Female sex	5328/8239 (64.7)
Children (including neonates)	645/5312 (12.1)
Clinical and radiological characteristics	
Headache	4833/6262 (77.2)
Focal neurological deficit	1986/4983 (39.9)
Seizures	2849/6670 (42.7)
Comatose	515/3292 (15.6)
Papilledema	1735/5073 (34.2)
Intracranial hemorrhage	1569/4537 (34.6)
Risk factors	
Pregnancy or puerperium ‡	1503/4587 (32.8)
Oral contraceptive use ‡	1238/3625 (34.2)
Infection	713/5773 (12.4)
Malignancy	287/5670 (5.1)
Trauma	125/4774 (2.6)
Therapy	
Anticoagulation	5348/7438 (71.8)
Endovascular thrombolysis	337/3669 (9.2)
Decompressive craniotomy	72/2022 (3.6)

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* *Categorical variables are given as n/N, where n is the number of patients in which the variable was present and N the total number of patients for which that particular variable was reported. The percentage is given within brackets. † Recalculated from data of 50 studies, including 6462 patients. The average age was used or, if not reported, the median age. ‡ Female patients only.*

RESULTS

Study characteristics

Our search identified 4585 articles, of which 178 were potentially eligible (Figure 1). Of these, 104 studies were excluded, mostly because of redundant data (n=31) or because data on mortality were lacking (n=45). Thus, 74 studies were included in the analysis, with data of 8829 patients with CVT recruited between 1942 and 2012 (Table I in the online-only Data). The number of patients per study varied between 40 and 706 (median 76; interquartile range, 56-138) and the duration of inclusion varied between 1 and 48 years (median 10; interquartile range, 5-13). For 7 studies

we assumed a inclusion period of 10 years because the time span was not reported. Sixteen (22%) studies were prospective, and 29 (39%) were multicenter. Studies originated mostly from India (15), United States (8), or Germany (6). Seventeen studies were performed in low or lower middle income countries. Nineteen studies reported on a selected category of patients, namely pregnant women (9 studies), children (7 studies, of which 3 included neonates only), patients treated with throm- bolysis (2 studies), and patients with Behcet's disease (2 studies).

Baseline characteristics and treatment

The average age of patients was 32.9 years, and 64.7% were women (Table 1). There were 645 pediatric cases (12.1%). The most common symptoms at baseline were headache (77.2%), seizures (42.7%), and focal neurological deficits (39.9%). At admission, 15.6% of patients were comatose, and an intracranial hemorrhage was present in 34.6%. Oral contraceptive use (34.2% of women) and pregnancy/puer- perium (32.8% of women) were the most common risk factors. Heparin was used in 54 of 74 studies (73%). In 9 studies (12%) no heparin was used, and 11 studies (15%) did not report whether heparin was used. In total, 71.8% of patients were treated with anticoagulation. Of the 54 studies in which patients were treated with heparin, 13 used unfractionated heparin, 3 used low-molecular-weight heparin, and 27 used both types. The type of heparin was not disclosed in 11 studies. Endovascular throm- bolysis was performed in 9.2% and decompressive craniotomy in 3.6% of patients.

Mortality

Seventy-one studies provided data on mortality at discharge, 23 at follow-up, and 20 studies reported both. The median duration of follow-up (reported in 18 studies) was 14 months (interquartile range, 3-31). There was a significant inverse correlation between mortality and year of patient recruitment (Pearson correlation coeffi- cient, -0.72; p<0.001, Figure 2 and Table 2). In the sensitivity analyses, exclusion of single-center studies, retrospective studies, studies from low-income countries, and pediatric studies, essentially yielded similar results. After exclusion of studies published before 1990, there was still a significant correlation between mortality and year of patient recruitment (Pearson correlation coefficient, -0.51; p<0.001), but if all studies published before 2000 were excluded, the correlation disappeared (Pearson correlation coefficient, -0.06; p=0.67). Reported mortality rates in studies published after 2000 ranged from 0% to 28%. We compared studies published after 2000 with a high mortality (>5%) with those with a low mortality (≤5%). Patients from studies with a high mortality were in a more severe clinical condition (coma, focal neurological deficits, and seizures all significantly more common). There were no significant differences between in study characteristics, risk factors or treatment.
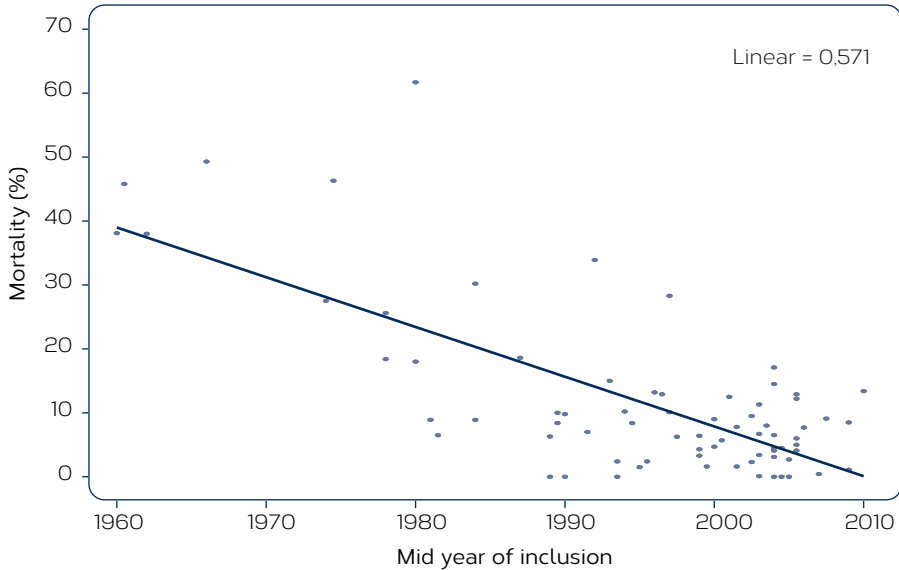
FIGURE 2. **Relation between mortality and year of the study.** *On the x axis, the year halfway of patient recruitment; on the y axis, the percentage mortality. Each dot indicates a single study.*

TABLE 2. Correlation between mortality and year of study.

	No. of Studies	No. of Patients	Correlation Coefficient	P value
Primary analysis	74	8829	−0.72	<0.001
Sensitivity analyses				
Multicenter studies	29	4676	−0.69	<0.001
Studies published >1990	65	8060	−0.51	<0.001
Studies published >2000	54	7268	−0.06	0.67
Studies from high-income countries	56	6150	−0.70	<0.001
Prospective studies	16	2686	−0.54	0.03
Duration of inclusion ≤10 y *	45	5424	−0.58	<0.001
Studies with adult patients only	61	7329	−0.76	<0.001
Studies with pediatric patients only	7	578	−0.63	0.13

For each analysis the Pearson correlation coefficient between mortality and time (of the study) is shown.

* Exclusion of studies with a time span of inclusion of >10 years or in which no time span is reported.

Potential explanatory factors

To examine which factors could explain the decline in mortality, we assessed the change in frequency of several parameters over time (Table 3). Both the frequency of focal neurological deficits and coma decreased significantly over time (correlation coefficient, –0.50; and –0.52, respectively). Trauma and infection-related CVT also decreased over time, although the latter was not significant.

TABLE 3. Potential explanatory factors for the decline in mortality.

	No. of Studies	No. of Patients	Correlation Coefficient	P value
Age *	50	6462	0.05	0.73
Coma	31	3292	-0.52	0.003
Focal neurological deficits	48	4983	-0.50	<0.001
Seizures	59	6670	-0.06	0.66
Intracerebral hemorrhage	39	4537	-0.28	0.12
Infection-related CVT	44	5773	-0.27	0.08
Malignancy-related CVT	43	5670	0.17	0.28
Traumatic CVT	40	4774	-0.42	0.007
Oral contraceptive use	56	6647	0.30	0.02

*The Pearson correlation coefficient between time (of the study) and the potential explanatory factor is given. * The average age was used or, if not reported, the median age.*

DISCUSSION

Our systematic review of the literature shows that the mortality of patients with CVT has substantially declined over time. There are several possible explanations for this finding. Part of the decline is probably the result of general improvement of hospital care. Similar trends in declining mortality have been found in other diseases, such as ischemic stroke[7] and pulmonary embolism.[8] However, the decline in mortality in CVT is too large to be solely explained by this factor. The factor that has probably contributed most to the decline in mortality is the improvement in radiological investigations. Before the invention of cerebral angiography, CVT could only be diagnosed with certainty at autopsy or surgery, which resulted in a selection bias of patients in a severe condition.[9] Even after introduction of angiography, many cases probably still went unnoticed because of the laborious and invasive nature of the procedure. Now that MRI (including magnetic resonance venography) and computed tomography venography have almost completely replaced cerebral angiography for the diagnosis of CVT, milder cases (e.g., patients with isolated headache) are more frequently identified. This hypothesis is supported by our finding

that the severity of the clinical condition of patients with CVT has also decreased over time (less coma and focal neurological deficits) and the increased incidence of CVT over time.[3, 10] In addition, if the analysis was restricted to studies published after 2000 – at which time use of computed tomography venography and MRI had become widespread – there was no longer a correlation between mortality and time of the study. A third factor which probably contributed to the decline in mortality is a shift in risk factors. We found that both traumatic and septic CVT have decreased over time, whereas the number of patients using oral contraceptives increased. The latter group is known to have a better prognosis[11], while sepsis–related CVT cases have a worse prognosis.[12] The final variable that may explain part of the decrease in mortality is the improved therapy for CVT. The introduction of anticoagulation and later decompressive hemicraniectomy probably had a positive effect on the survival of patients.[13, 14] Unfortunately, we could not extract individual patient data from the studies and thus were unable to correlate data on mortality or hemorrhagic compli-cations to the different types of heparin.

One of the strengths of our study is the very large number of patients with CVT who were included and the robustness of data collection. We used a broad search strategy and the entire screening process was performed independently by 2 people. The demographics, clinical manifestations and risk factors also suggest that our study included a sample of patients that is representative for CVT.[5] One of the weaknesses of the study is that we could include only a limited number of old studies, which was partly attributable to the fact that we excluded studies with <40 patients. Because this could bias the results, we confirmed our findings in studies published after 1990. Unfortunately, the majority of studies did not provide mortality at follow–up, and therefore there were insufficient data to analyze long–term mortality.

In conclusion, we have found a clear trend in declining mortality among patients with CVT over time, which is most likely explained by improvements in therapy, a shift in risk factors, and, most importantly, the identification of less severe cases

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SUPPLEMENTAL TABLE 1. Study characteristics and references of included studies.
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First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Pai[1]	2013	2001-2010	India	P/M	612
Qu[2]	2013	2002-2007	China	R/S	62
Jalili[3]	2013	1997-2009	Iran	R/S	62
Dentali[4]	2012	2002-2012	Italy	R/M	706
Coutinho[5]	2012	2008-2010	The Netherlands	R/M	94
Wasay[6]	2012	2001-2008	Pakistan	R/M	204
Uzar[7]	2012	2008-2010	Turkey	R/S	47
Kalita[8]	2012	1995-2011	India	R/S	90
Sartori[9]	2012	1998-2007	Italy	P/S	44
Misra[10]	2012	2005-2010	India	P/S	66
Narayan[11]	2012	2002-2010	India	P/S	428
Hinnell[12]	2012	1999-2009	Canada	R/S	108
Chiquet[13]	2012	2010-2010	Mexico	R/M	194
Ruiz-Sandoval[14]	2011	2002-2004	Mexico	P/M	59
Kumral[15]	2011	1998-2010	Turkey	R/S	220
Algahtani[16]	2011	1990-2010	Saudi Arabia	R/M	111
Ashjazadeh[17]	2011	2000-2008	Iran	R/S	124
Moharir[18]	2011	1992-2009	Canada	P/M	104
Vembu[19]	2011	2000-2010	Kuwait	R/S	71
Santos[20]	2011	2004-2007	Portugal	R/S	49
Halesha[21]	2011	2005-2006	India	R/S	50
Grunt[22]	2010	2000-2008	Switzerland	P/M	65
Sahraian[23]	2010	2003-2008	Iran	P/M	41
Aaron[24]	2010	1999-2009	India	P/S	41
Putaala[25]	2010	1990-2008	Finland	R/S	91
Jordan[26]	2010	2003-2007	Canada	P/M	84
Rizzo[27]	2010	1996-2006	Italy	R/S	40

First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Vieira[28]	2010	2001–2007	Portugal	R/M	53
English[29]	2009	1995–2004	US	R/S	61
Saadatnia[30]	2009	2001–2006	Iran	R/M	162
Yesilot[31]	2009	1984–2006	Turkey	R/S	68
Saadou[32]	2009	1974–2006	France	R/S	64
Damak[33]	2009	1997–2006	France	P/S	62
Li[34]	2009	1998–2008	China	R/S	168
Khealani[35]	2008	1991–2007	Pakistan	R/M	109
Nagaraja[36]	2008	2005–2006	India	R/S	60
Wasay[37]	2008	1991–2001	US	R/M	182
Wasay[38]	2008	1992–2001	US	R/M	70
Libourel[39]	2007	1999–2006	The Netherlands	R/S	63
Nagaraja[40]	2007	2003–2005	India	R/S	96
Dindagur[41]	2006	1995–2005	India	R/S	172
Gosk-Bierska[42]	2006	1978–2001	US	R/S	154
Masuhr[43]	2006	1976–2004	Germany	P/M	194
Anand[44]*	2006	1995–1999	India	R/S	99
Anand[44]*	2006	2000–2003	India	R/S	180
Fitzgerald[45]	2006	1986–2005	US	R/S	42
Stolz[46]	2005	1985–2001	Germany	R/S	79
Ferro[47]	2004	1998–2001	Portugal	P/M	624
Bergui[48]	2003	1993–2002	Italy	R/S	48
Mehraein[49]	2003	1992–2002	Germany	R/S	79
Wasay[50]	2001	1981–1997	US	R/M	40
DeVeber[51]	2001	1992–1997	Canada	P/M	160
Ferro[52]	2001	1980–1998	Portugal	R/M	142
Lanska[53]	2000	1993–1994	US	R/M	170
Saw[54]	1999	1986–1997	Australia	R/S	42
de Bruijn[55]	1999	1992–1996	The Netherlands	P/M	59

First Author	Year of publication	Period of inclusion	Country lead author	Study design	No. of patients
Brucker[56]	1998	1991–1996	Germany	R/M	42
Nagaraja[57]	1998	1987–1997	India	R/S	56
Daif[58]	1995	1985–1994	Saudi Arabia	R/M	40
Bienfait[59]	1995	1970–1990	The Netherlands	R/M	62
Cantu[60]	1993	1982–1992	Mexico	R/S	113
Diaz[61]	1992	1942–1990	US	R/M	203
Einhaupl[62]	1991	1977–1991	Germany	P/M	43
Bousser[63]	1991	1975–1988	France	R/S	76
Karabudak[64]	1990	1979–1989	Turkey	R/S	56
Samuel[65]	1987	1978–1984	South Africa	R/S	45
Gates[66]	1986	1975–1985	Australia	R/M	47
Rousseaux[67]	1985	1973–1983	France	R/S	49
Srinivasan[68]	1983	1974–1982	India	R/S	135
Nagpal[69]	1983	1967–1982	India	S/R	80
Bansal[70]	1980	1969–1997	India	S/R	138
Huhn[71]	1971	1951–1970	Germany	R/S	120
Krayenbuhl[72]	1968	1957–1967	Switzerland	R/S	92
Weber[73]	1966	1955–1965	Unknown	R/S	63

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* This study describes 2 different time spans of patient inclusion. P indicates prospective; R, retrospective; M, multi-center; S, single-center.

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5

PART II

Clinical course and outcome

6

CLINICAL COURSE OF CEREBRAL VENOUS THROMBOSIS IN ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA

Susanna M. Zuurbier*, Mandy N. Lauw*, Jonathan M. Coutinho
Charles B.L.M. Majoie, Bronno van der Holt, Jan J. Cornelissen
Saskia Middeldorp, Bart J. Biemond, Jan Stam

Contributed equally

ABSTRACT

Background

Venous thromboembolism (VTE) is a frequent complication in patients with acute lymphoblastic leukaemia (ALL). A significant proportion of patients develop cerebral venous thrombosis (CVT).

Methods

To investigate risk factors for and the clinical course of CVT in ALL patients, we describe all cases of CVT which occurred in a well-defined cohort of 240 adults, treated for newly diagnosed ALL in the HOVON (Dutch-Belgian Hemato-Oncology Cooperative Group)-37 study. We conducted a nested case-control study to explore the relevance of early symptoms and risk factors for CVT in ALL patients.

Results

Nine of 240 patients developed CVT (4%). CVT occurred during or shortly after L-asparaginase therapy (in 8 cases) and shortly after intrathecal methotrexate injections (in all cases) during Cycle I of remission induction treatment. CVT was associated with prior headache and seizures. In 5 of 9 patients with CVT, headache prior to the diagnosis of CVT occurred within 3 days after lumbar puncture and initially had a postural character.

Conclusions

CVT is relatively common in adult ALL patients. Our data suggest that CVT in adult ALL patients results from the additive effects of multiple risk factors, with a particular role for asparaginase and the effects of lumbar punctures for intrathecal therapy.

INTRODUCTION

Venous thromboembolism (VTE) is a well-known complication in patients with acute lymphoblastic leukaemia (ALL). Reported incidences vary between 1% and 36%, depending on the investigated patients (adults or children), treatment protocol, the inclusion of asymptomatic or symptomatic VTE, and whether the study design was prospective or retrospective.[1-5] VTE causes mortality, morbidity and the premature discontinuation of ALL therapy. Remarkably, up to 50% of patients with VTE in ALL have cerebral venous thrombosis (CVT),[1-3, 6-8] although the general incidence of CVT is low.[9]

The increased risk of VTE in patients with ALL has been attributed to multiple factors,[10] such as components of the treatment, particularly steroids and L-asparaginase.[1, 6, 11] Prothrombotic changes induced by the ALL itself may also contribute to the risk of VTE,[11] whereas thrombophilic mutations may provide an additional thrombotic risk.[1, 6, 10, 12]

Although CVT constitutes a large proportion of VTE in ALL, the absolute number of events is small and limited data are available on the presentation, clinical course and outcome of CVT in the context of ALL. We examined all CVT events that occurred in a well-defined cohort of adult patients treated for ALL in the HOVON (Dutch-Belgian Hemato-Oncology Cooperative Group)-37 study. Data on the incidence and prevention of VTE in the HOVON-37 ALL study have been published previously.[5] In this study, we focus on the clinical course, potential risk factors and relevance of early symptoms of CVT in patients within this cohort.

METHODS

Study population and ALL treatment protocol
We retrospectively analysed patients treated in the Dutch-Belgian HOVON-37 ALL (HO37) study, a prospective, multicentre, phase II study that investigated the value of early intensification by allogeneic or autologous stem cell transplantation in ALL treatment (registered at www.trialregister.nl as NTR228).[5, 13] Briefly, 240 adult patients (16-59 years) with newly diagnosed ALL or lymphoblastic lymphoma were included between April 1999 and November 2005. All patients received the same 3 cycles of combination chemotherapy according to the study protocol, before assessment for stem cell transplantation. Cycle I consisted of daily prednisone 60 mg/m^2 (days 1-28), daunorubicin 45 mg/m^2 and vincristine 1.5 mg/m^2 (days 1, 8, 15 and 22), and L-asparaginase 5000 IU/m^2 (days 15-28). In addition, at least 3 intrathecal injections of 15 mg methotrexate (MTX) were administered as central nervous system (CNS) prophylaxis. None of the patients received (low-molecular-weight) heparin for thromboprophylaxis. All women of fertile age received lynestrenol or other

progestogenic agents to prevent (menstrual) blood loss. The study was performed in accordance with the Declaration of Helsinki and approved by the medical ethics committee. Written informed consent was obtained from all patients.

Study design

All occurrences of VTE during treatment were identified and recorded prospectively as serious adverse events on case report forms. For all patients with CVT, we systematically extracted data from patients' medical and nursing records. The diagnosis of CVT was re-evaluated by examination of imaging results by an independent neuroradiologist (CBLMM). We qualitatively describe characteristics of CVT events and ALL patients with CVT. The following variables in patients with CVT were described; radiological characteristics, temporal relationships with treatment components and potential etiological factors, and clinical outcome. Temporal relationship with ALL treatment was analyzed by calculating days between CVT diagnosis and the last administration date of the various chemotherapeutic agents. To explore the relevance of early symptoms for CVT (headache, seizures, neurological deficits) in ALL patients, we conducted a nested case-control study. For each CVT case we selected 2 control patients without CVT from within the HO37 and analyzed the presence of headache, seizures or neurological deficits before the diagnosis of CVT. Controls were matched by treatment center, sex, ALL type and risk classification (standard versus poor risk), and age (± 5 years).

Definitions

VTE was defined as a clinically symptomatic venous thrombosis or pulmonary embolism, confirmed by standard imaging tests. Screening for asymptomatic VTE was not performed. CVT was defined as an intraluminal filling defect or presence of a thrombus in one of the cerebral veins or sinuses, detected with magnetic resonance venography, computed tomographic venography or angiography. Complete remission (CR) was defined as normocellular marrow containing less than 5% blast cells by morphology and immunophenotyping, no peripheral blood leukaemic cells, and no evidence of extramedullary disease. Patients were classified with a poor risk ALL in case of presence of cytogenetic abnormalities (t(9;22), t(4;11), or t(1;19)), pro–B-cell immunophenotype, and high white blood cell count (ie, >30 x 10^9/L in case of B-cell ALL; >100 x 10^9/L in case of T-cell ALL).

Statistical analysis

Differences between patients with and without CVT were analysed by Fisher exact or Mann-Whitney tests. The relevance of early symptoms for CVT in ALL patients was expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Associations between occurrence of CVT and the likelihood to achieve CR were explored by multivariate logistic regression analysis. We used IBM SPSS Statistics (IBM, Armonk, NY, USA) version 19.0 for Windows and Stata Statistical Software (StataCorp LP, College Station, TX, USA) release 11 for analyses.

RESULTS

Patients

Among 240 ALL patients in the HO37, 24 patients experienced VTE (10%), of whom 9 developed CVT (4%; 38% of all VTE).[5] Median age of patients with CVT was 33 years (range, 17-49); 5 were women; 5 patients were treated for B-ALL and 4 for T-ALL. Four patients with CVT were classified as a poor risk ALL (cases 3, 5, 6 and 8); 1 patient with CVT had CNS infiltration of the ALL (case 7). Patient and disease characteristics did not differ significantly between patients with and without CVT (Table I). The remaining VTE episodes were upper limb vein thrombosis (n=11), deep vein thrombosis (DVT) of the leg (n=3), and 1 case of pulmonary embolism. Thus, the ratio of CVT to leg-vein DVT was 3:1, and 7 of 9 patients with CVT were evaluated for the presence of thrombophilic factors (prothrombin G20210A mutation, factor V Leiden mutation, and lupus anticoagulant). One patient tested positive for lupus anticoagulant on 2 occasions (case 7). None of the patients carried the prothrombin G20210A or factor V Leiden mutation. No patient had meningitis, sinusitis or other concurrent cranial infections at the time CVT occurred. None of the patients had a history of previous VTE.

TABLE 1. Patient and disease characteristics by distribution of occurrence of CVT in the HOVON-37 ALL multicenter study.

Patient and disease characteristics	Patients with CVT (n=9)	Patients without CVT (n=231)
Median age at inclusion, y (range)	33 (17-49)	33 (16-59)
Female, n (%)	5 (56)	89 (39)
ALL subtype		
B-lineage ALL	5 (56)	176 (76)
T-lineage ALL	4 (44)	50 (22)
Other/unknown	0	5 (2)
Prognostic risk classification		
Standard	5 (56)	129 (56)
Poor *	4 (44)	102 (44)
CNS infiltration of ALL	1 (11)	20 (9)
Median WBC count at inclusion (range)	10.5×10^9/L (1.0-34.0)	12.0×10^9/L (0.5-878.0)
Median platelet count at inclusion (range)	178×10^9/L (26-571)	54×10^9/L (5-652)
CR after cycle I	4 (44)	191 (83)
CR after treatment protocol	5 (56)	209 (90)

* Based on presence of cytogenetic abnormalities (t(9;22), t(4;11), or t(1;19)), pro- B- cell immunophenotype, and high WBC count (i.e. >30x10⁹ /L in case of B-cell ALL; >100x109 /L in case of T-cell ALL). ALL indicates acute lymphoblastic leukaemia; CNS, central nervous system; CR, complete remission; CVT, cerebral venous thrombosis; WBC, white blood cell; significant p values are marked in bold.

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Radiological characteristics of CVT

CVT was diagnosed by magnetic resonance venography in 5 patients and by computed tomographic venography in 4. CVT was located in the superior sagittal sinus in 8 of 9 patients; in 3 patients, multiple sinuses were affected (Table 2). Seven patients had cerebral parenchymal lesions (5 hemorrhagic infarcts and 2 non-hemorrhagic infarcts). Two patients (cases 3 and 8) had a significant mass effect of the hemorrhagic infarct, resulting in a midline shift of 7 and 2 mm, respectively.

TABLE 2. Radiological characteristics on CVT diagnosis detected with imaging.

Characteristics	Patients with CVT (n=9)
Location	
Superior sagittal sinus	8
Transverse sinus left and/or right	3
Sigmoid sinus left and/or right	1
Straight sinus	1
Cortical vein	7
Cerebral parenchymal lesions	7
Hemorrhagic	5
Non-hemorrhagic	2
Midline shift (n)	2

CVT indicates cerebral venous thrombosis.

Temporal relationships with ALL treatment

All CVT cases occurred during cycle 1 of remission induction treatment. The median interval from the start of ALL treatment to the diagnosis of CVT was 21 days (range, 13-33). In 8 of 9 cases, CVT occurred in close temporal association with L-asparaginase therapy: 7 during L-asparaginase therapy and 1 just after (case 9; Figure 1). One CVT occurred before the patient was exposed to L-asparaginase (case 1); the drug was withheld from this patient during later stages of treatment. L-asparaginase was prematurely discontinued in Cycle 1 due to CVT in 6 of the 7 patients in whom CVT occurred during its administration, and delayed in 1 (case 2). The median interval between the last L-asparaginase administration and CVT was 0 days (range 0-3).

All patients with CVT also received at least 1 intrathecal injection of MTX therapy by lumbar puncture at the time of CVT diagnosis (Figure 1). The median interval between the last intrathecal MTX administration and the diagnosis of CVT was 6 days (range 1-13).
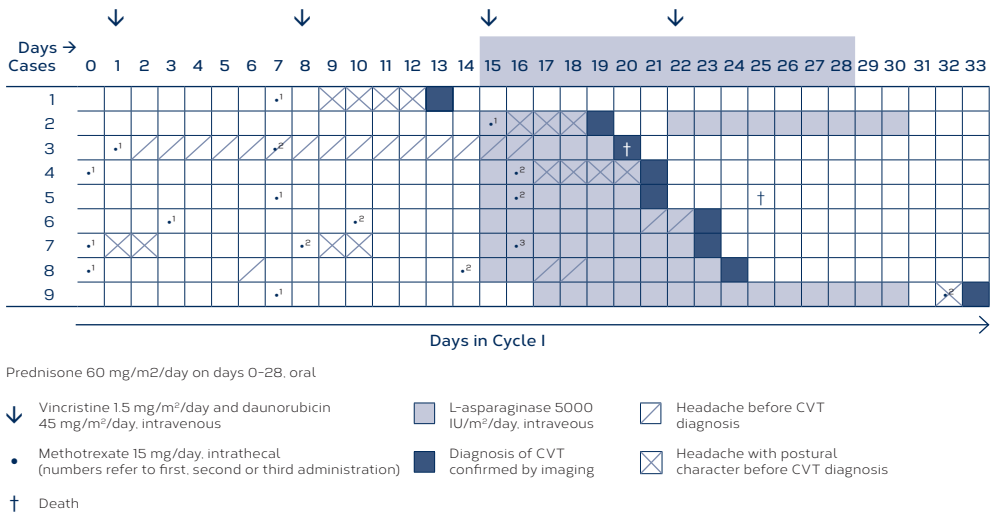
FIGURE 1. Temporal relationships between cerebral venous thrombosis (CVT) diagnosis and acute lymphoblastic leukaemia (ALL) treatment in HOVON-37 study cycle I.

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Clinical Outcome of CVT and of ALL

After the diagnosis of CVT, 8 patients were treated with therapeutic doses of (low-molecular-weight) heparin. In 1 patient with a large hemorrhagic infarct, anticoagulant treatment was not given (case 8). Two patients were treated additionally with endovascular thrombolysis (cases 3 and 5). These patients had severe hemorrhagic lesions before treatment and both died in the acute phase because of transtentorial herniation by increased hemorrhage. Another patient (case 8, not treated with the anticoagulant) also had an increase of the hemorrhagic infarct, whereas 2 patients (cases 2 and 9) had an increase of non-hemorrhagic infarcts during anticoagulant treatment.

Two patients with CVT had recurrent VTE (cases 2 and 7), none a recurrent CVT. Five patients with CVT died in the first 12 months of their HO37 treatment (2 after thrombolysis for CVT treatment, 2 because of ALL progression and 1 because of nonrelapse ALL-related mortality). The overall mortality (all ALL cases) at 12 months was 29%. Patients with CVT less often obtained CR than patients without CVT, both after Cycle I (44% versus 83%; OR, 0.17; 95% CI, 0.04-0.65) and after the complete treatment protocol (56% versus 90%; OR, 0.13; 95% CI, 0.03-0.53). Adjustment for poor ALL risk did not alter this (adjusted OR, 0.17; 95% CI, 0.04-0.65 after Cycle I; adjusted OR, 0.12; 95% CI, 0.03-0.51 after complete protocol). At 3-month neurological follow-up, occasional headache was documented in 3 of the 6 surviving patients (cases 1, 4, and 6), another seizure in Cycle III in 1 patient (case 2), and remaining neurological deficits (hemiparesis) in 2 patients (cases 2 and 8).

Relevance of early symptoms for CVT in ALL patients

Headache was documented in 8 of the 9 patients before CVT diagnosis and in 4 of the 18 matched controls without CVT (OR 28; 95% CI, 3–296). Headache in CVT patients was reported as severe and persistent. In 6 CVT patients, headache was present within 4 days before the diagnosis of CVT. In 5 cases, the headache commenced within 3 days after lumbar puncture and initially had a postural character, that is increased severity of headache in vertical position. Median time between headache onset and the diagnosis of CVT was 4 days (range 0–19; Figure 1). In the 4 controls, headache was bilateral and remitting, also was postural initially, and began within 24 hours after lumbar puncture. In 2 controls, it prompted diagnostic imaging of the brain, without any signs of CVT. Seizures occurred in 8 of 9 patients with CVT and in none of the controls (OR∞). Focal neurological deficits developed in 6 of 9 patients with CVT and in 3 of 18 controls (OR, 10; 95% CI, 2–64). Neurologic deficits in the controls were caused by CNS infiltration of ALL (2 cases) and by a subdural haematoma (1 case).

DISCUSSION

Although CVT is a rare kind of thrombosis, it is relatively common in adult ALL patients, occurring in 9 of the 240 patients (4%) in our study. Two patients with CVT died in the acute phase because of the consequences of CVT. CVT was also associated with a worse outcome of ALL treatment, indicated by lower rates of CR in patients with CVT.

In the general population, the incidence of CVT is 1.7/100.000 per year for people aged 15–49 years.[9] A Mayo Clinic study reported a DVT (leg veins) incidence of approximately 27/100.000 per year for people aged 15–49 years.[14] Hence, one would expect 1 case of CVT for each 16 cases of DVT, which is strikingly different from the 3:1 ratio we observed in ALL patients (9 cases of CVT versus 3 with leg-vein DVT). Upper limb vein thrombosis, generally much rarer than DVT of the leg, was also observed more frequently among ALL patients in the HO37 cohort.[5] Therefore, it is likely that, against a strongly increased background risk of VTE in ALL patients treated with L-asparaginase, additional local factors cause these rarer forms of VTE. For upper limb vein thrombosis, this local factor is very likely the use of central venous catheters; for CVT, this is less obvious.

One of these factors might be the intrathecal MTX administration. Patients with CVT had received at least 1 intrathecal injection of MTX. Inflammatory effects of MTX may induce local thrombosis.[8, 15] However, in the GIMEMA study, no intrathecal MTX was administered but the incidence of CVT during the first remission induction cycle was still 2.1%.[16] The increased risk may also be explained by effects of the intrathecal administration. Lumbar punctures may cause low cerebrospinal

fluid pressure,[17] causing a downward displacement of the brain and traction on the cortical veins and the superior sagittal sinus. The fact that the thrombus was located in the superior sagittal sinus in 8 of our 9 CVT cases, which is more common than in general CVT,[15, 18, 19] supports this explanation. Five of our patients with CVT had postural headache – indicating low CSF pressure – during 3 days after the lumbar puncture. Although the frequency of postural headache after lumbar puncture varies – depending on the type and size of the needle[20, 21] – the percentage (56%; i.e. 5 of 9) is quite high. Our small number of cases does not allow a proper risk factor analysis, but this observation supports the hypothesis that intrathecal MTX administration may contribute to ALL-associated CVT.

Additionally, 8 of 9 CVT events occurred during or shortly after L-asparaginase therapy in cycle I of induction treatment (range 0-2), which suggests a causal rela-tionship. ALL studies without asparaginase, such as the hyper-CVAD regimen indeed do not report VTE complications.[22] However, protocols including asparaginase provide a survival advantage over those without and are more commonly used.[22, 23] After cycle I, L-asparaginase or intrathecal MTX therapy was not complicated by CVT. Therefore, other factors during the first induction cycle, such as use of steroids, leukaemia activity or tumour lysis, may also contribute to the pathogenesis of CVT.

Delay of asparaginase therapy or lumbar punctures beyond the first treatment cycle might prevent CVT, but with the risk of lower remission rates.[23] Thromboprophylaxis during high-risk medication in ALL induction treatment might prevent VTE.[5] However, it also increases the risk of bleeding, and the efficacy and optimal approach of thromboprophylaxis remain unclear because of a lack of randomized trials in patients with ALL, particularly in adults.[1, 5]

Our study has several limitations. The absolute number of CVT cases is small, and the analysis is retrospective and observational. Hence, estimated associations between prodromal symptoms and CVT are limited by insufficient statistical power to adjust for confounders. Moreover, our case-control study was not intended to examine etiological risk factors for CVT, as we matched cases with CVT and controls for some of these risk factors. Other potential risk factors for CVT, such as treatment components, were only presented in a descriptive manner. Furthermore, our study population was treated within the HO37 trial, with specific inclusion and exclusion criteria and treatment protocol, limiting the external validity of our results. Finally, the HO37 was not intended for neurological analysis. Neurological symptoms were not included in case report forms, and we were not able to retrieve prevalence of head-ache across the entire HO37 cohort, but only for the cases and selected controls.

In summary, our study shows that CVT is a relatively common thrombotic compli-cation in adult patients with ALL, associated with a high mortality rate and a worse result of ALL treatment. The majority of CVT occurred in close relation

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with L-asparaginase and intrathecal MTX therapy in cycle I of induction treatment. Similarly to non-ALL related CVT, headache and seizures were strongly associated with occurrence of CVT. Hence, close monitoring of headache during ALL treatment may contribute to earlier detection of CVT and could improve its outcome.

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7

ADMISSION HYPERGLYCEMIA AND CLINICAL OUTCOME IN CEREBRAL VENOUS THROMBOSIS

Susanna M. Zuurbier*, Sini Hiltunen*, Turgut Tatlisumak
Guusje M. Peters, Suzanne M. Silvis, Elena Haapaniem, Nyika D. Kruyt
Jukka Putaala, Jonathan M. Coutinho
* Contributed equally

ABSTRACT

Background
Admission hyperglycemia is associated with poor clinical outcome in ischemic and hemorrhagic stroke. Admission hyperglycemia has not been investigated in patients with cerebral venous thrombosis.

Methods
Consecutive adult patients with cerebral venous thrombosis were included at the Academic Medical Center, The Netherlands (2000–2014), and the Helsinki University Central Hospital, Finland (1998–2014). We excluded patients with known diabetes mellitus, and patients without known admission blood glucose. We defined admission hyperglycemia as blood glucose ≥7.8 mmol/l (141 mg/dl), and severe hyperglycemia as blood glucose ≥11.1 mmol/l (200 mg/dl). We used logistic regression analysis to determine if admission hyperglycemia was associated with modified Rankin Scale (mRS) score of 3 to 6 or mortality at last follow-up. We adjusted for: age, sex, coma, malignancy, infection, intracerebral hemorrhage, deep cerebral venous thrombosis, and location of recruitment.

Results
Of 380 patients with cerebral venous thrombosis, 308 were eligible. Of these, 66 (21.4%) had admission hyperglycemia with 8 (2.6%) having severe admission hyperglycemia. Coma (31.3% versus 5.0%, p<0.001) and intracerebral hemorrhage (53.0% versus 32.6%, p=0.002) at presentation were more common among patients with admission hyperglycemia than normoglycemic patients. Patients with admission hyperglycemia had a higher risk of mRS 3–6 (adjusted odds ratio, 3.10; 95% confidence interval, 1.35–7.12), and mortality (adjusted odds ratio, 4.13; 95% confidence interval, 1.41–12.09). Severe hyperglycemia was even more strongly associated with mRS score of 3 to 6 (adjusted odds ratio, 11.59; 95% confidence interval, 1.74–77.30) and mortality (adjusted odds ratio, 33.36; 95% confidence interval, 3.87–287.28) compared to normoglycemic patients.

Conclusions
Admission hyperglycemia is a strong predictor of poor clinical outcome in patients with cerebral venous thrombosis.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare cause of stroke, which mostly affects children and young adults.[1, 2] The mortality of CVT has decreased steadily in the past decades and is now ≈5% to 10%.[3] Many predictors of poor clinical outcome have been identified in CVT. In the International Study on Cerebral Vein and Dural sinus Thrombosis, older age, male sex, mental status disorder, coma, thrombosis of the deep venous system, intracranial hemorrhage, cancer, and infection of the central nervous system were independently associated with death or dependency at last follow-up.[4] Other studies showed that hydrocephalus and focal neurologic deficit are also associated with a poor outcome.[5, 6]

Admission hyperglycemia is a common finding in ischemic and primary intracerebral hemorrhagic stroke, as well as in subarachnoid hemorrhage, with frequencies of ≤63% among non-diabetic patients.[7] Various studies have found that admission hyperglycemia is associated with a poor clinical outcome and increased mortality in patients with these various types of stroke.[8-14] However, to our knowledge, this association has not been studied in CVT. The aim of our study was to determine if admission hyperglycemia is a risk factor for poor outcome in patients with CVT.

METHODS

Patient identification and selection

In this retrospective cohort study, we included adult patients with CVT from 2 academic hospitals: the Academic Medical Center (Amsterdam, the Netherlands) and the Helsinki University Central Hospital (Finland). Both the centers maintain a database with detailed information on consecutive patients with CVT since January 2000 (Amsterdam) and January 1998 (Helsinki). In the Academic Medical Center, data of these patients have been collected prospectively since July 2006. Patients from January 2000 to July 2006 were identified retrospectively using International Classification of Diseases Tenth Revision codes and the Dutch financial coding system for hospital care, as described previously.[5] The Helsinki database contains data from all consecutive patients admitted from 1998, identified retrospectively using International Classification of Diseases Tenth Revision codes from the hospital's electronic discharge register. From both the databases, we included patients admitted until December 2014. CVT was confirmed with computed tomography venography, magnetic resonance imaging with magnetic resonance venography, catheter angiography, or autopsy in all patients, in accordance with international standards.[15] We excluded patients with a history of diabetes and patients without known admission glucose concentration. Written informed consent was not obtained, because this is not required under Dutch or Finnish law in studies in which only anonymous observational data are used.

Data collection

Nonfasting glucose was determined as part of routine medical care. We used the first glucose concentration that was determined, but always within 24 hours of admission. For patients admitted through the emergency room (all patients except in-hospital CVT cases), this was generally done within 3 hours of presentation. For patients with an in-hospital CVT, we used the first glucose measurement after the diagnosis of CVT was established. Determination of glucose concentration was done on a Roche Cobas 8000 analyzer (Amsterdam) and a Roche Modular P analyzer (Helsinki). Both participating hospitals use a standardized sliding scale subcutaneous insulin regimen protocol for the monitoring and treatment of in-hospital hyperglycemia in patients with acute stroke.

For the prospective part of the Amsterdam database (2006–2014), baseline data of included patients were recorded at the time of admission on a case report form. For all other patients this information was extracted from the medical records.

Definition of admission hyperglycemia

Similar to previous studies, we defined admission hyperglycemia as a blood glucose concentration ≥7.8 mmol/l (141 mg/dl) and severe hyperglycemia as blood glucose ≥11.1 mmol/l (200 mg/dl).[16]

Clinical outcome

The clinical outcome was assessed with the modified Rankin Scale (mRS) during routine follow-up clinic visits. Patients with missing mRS from the retrospective period of the Amsterdam database were contacted by telephone between 2011 and 2012 to determine the score on the mRS using a structured interview.[17] Poor outcome was defined as a score of 3 to 6 on the mRS at last follow-up. All cause mortality at last follow-up was also analyzed separately.

Statistical analysis

We compared patients with hyperglycemia to those without hyperglycemia. Continuous data are provided as a mean with SD, or, if the data did not have a normal distribution, as a median with interquartile range. Categorical variables are given as n/N, where n is the first number of patients in which the variable was present, and the second N the total number of patients for which that particular variable was reported. The percentage is shown in parentheses.

For comparison of continuous data, we used a Student's T or Mann–Whitney U test and for categorical data a χ^2 or Fisher exact test, whichever was appropriate. The association between hyperglycemia and clinical outcome was studied using multivariate logistic regression analysis. We used mortality and mRS score of 3 to 6 at last follow-up as dependent variables. All multivariate analyses are adjusted for the following potential confounders: age, sex, coma, malignancy, infection, intracerebral

hemorrhage, deep CVT, and location of recruitment (Helsinki or Amsterdam). We also analyzed the data using glucose concentration as a continuous variable, and by stratifying patients into those with normoglycemia (<7.8 mmol/l, <141 mg/dl [reference category in the multivariate analysis]), admission hyperglycemia (7.8 – 11.0 mmol/l, 141 – 199 mg/dl), and severe admission hyperglycemia (≥11.1 mmol/l, ≥200 mg/dl). All data were analyzed with SPSS version 20 (IBM Inc., Armonk, NY, USA). A 2-tailed p<0.05 was considered significant.

RESULTS

There were 380 adult patients with CVT admitted during the study period (n=194 Amsterdam cohort, n=186 Helsinki cohort, Figure 1). We excluded 60 patients because of missing baseline glucose concentration and 12 patients because they had a history of diabetes mellitus. Therefore, 308 patients (81% of all patients with CVT) were included in the analysis. An intracerebral hemorrhage at admission was less common in excluded patients (21% versus 37%, p=0.009), but other baseline characteristics and treatment details did not differ between the included and excluded patients (Table I in the online-only Data Supplement).
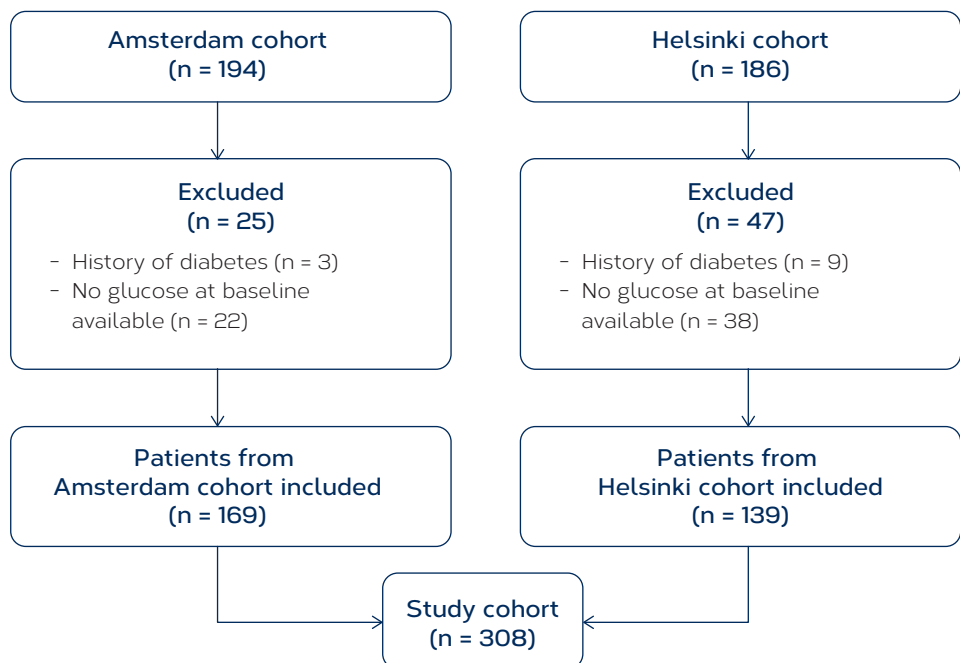

FIGURE 1. Flowchart of patient selection.

TABLE 1. Baseline characteristics and treatment details.

	Admission Hyperglycemia (n=66)	No Admission Hyperglycemia (n=242)	P value
Demographics			
Female (%)	40/66 (60.6)	180/242 (74.4)	0.03
Mean age (SD)	45.6 (15.6)	39.1 (14.8)	0.002
Symptoms and signs			
Headache	53/65 (81.5)	206/240 (85.8)	0.39
Focal neurological deficit	38/64 (59.4)	149/240 (62.1)	0.69
Seizure(s)	23/65 (35.4)	74/240 (30.8)	0.49
Coma (GCS <9)	20/64 (31.3)	12/238 (5.0)	<0.001
Papilledema	11/42 (26.2)	44/151 (29.1)	0.71
Days between admission & diagnosis (median, IQR)	1 (0-3)	0 (0-1)	0.98
Days between symptom onset & diagnosis (median, IQR)	4 (1-8)	5 (2-9)	0.98
Mode of onset			
Acute (<48 h)	19/64 (29.7)	68/236 (28.8)	0.89
Subacute (48 h to 30 d)	41/64 (64.1)	152/236 (64.4)	0.86
Chronic (>30 d)	3/64 (4.7)	16/236 (6.8)	0.54
Risk factors			
Previous thrombosis	7/66 (10.6)	17/241 (7.1)	0.34
Genetic thrombophilia	4/51 (7.8)	31/219 (14.2)	0.23
Inflammatory bowel disease	2/66 (3.0)	10/242 (4.1)	0.68
Previous infection	11/63 (17.5)	43/239 (18.0)	0.92
Malignancy	5/66 (7.6)	16/241 (6.6)	0.79
Thrombotic medication	7/66 (10.6)	31/241 (12.9)	0.62
Parenchymal lesions			
Intracerebral hemorrhage or hemorrhagic infarct	35/66 (53.0)	79/242 (32.6)	0.002
Brain edema	19/66 (28.8)	78/242 (32.2)	0.60
Any parenchymal lesion	46/66 (69.7)	135/242 (55.8)	0.04
Treatment			
Intensive care unit admission	39/66 (59.1)	57/242 (23.6)	<0.001
Insulin therapy	14/66 (21.2)	13/242 (5.4)	<0.001
Anticoagulation	59/66 (89.4)	237/242 (97.9)	0.001
Endovascular treatment	10/66 (15.2)	27/242 (11.2)	0.38
Decompressive hemicraniectomy	13/66 (19.7)	9/242 (3.7)	<0.001

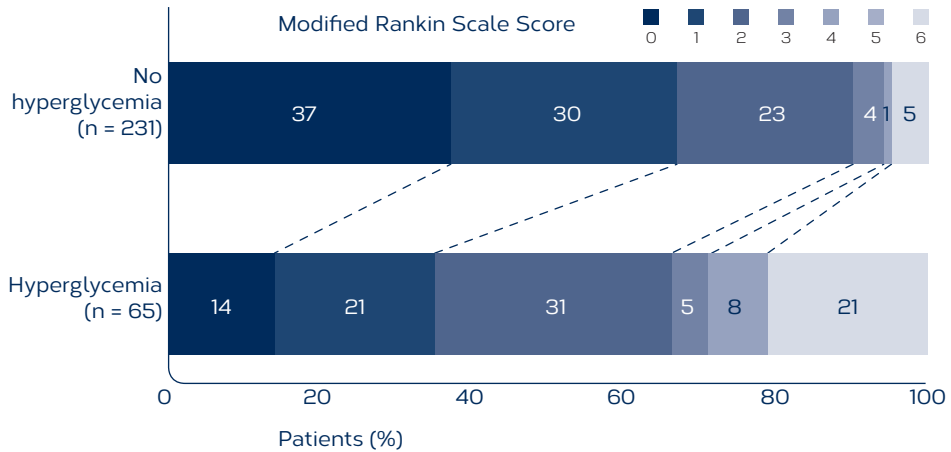*GCS indicates Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation.*

FIGURE 2. **Clinical outcome.** *Scores on the modified Rankin Scale (mRS) at last follow up are shown for patients with and without admission hyperglycemia. For each score, the percentage is shown in the bars. No patient in either group had a mRS of 5. Outcome data were not available for 12 patients (1 with admission hyperglycemia and 11 without admission hyperglycemia).*

TABLE 2. Association between admission hyperglycemia and clinical outcome.

	Admission Hyperglycemia	No Admission Hyperglycemia	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
mRS, 3–6	22/65 (33.8%)	24/231 (10.4%)	4.41 (2.27–8.58)	3.10 (1.35–7.12)
Mortality	14/66 (21.2%)	12/242 (5.0%)	5.16 (2.26–11.81)	4.13 (1.41–12.09)

The multivariate model is adjusted for age, sex, coma, malignancy, infection, intracerebral hemorrhage, deep cerebral venous thrombosis, and location of recruitment. Outcome data were not available for 12 patients (1 with admission hyperglycemia and 11 without admission hyperglycemia). CI indicates confidence interval; mRS, modified Rankin Scale; OR, odds ratio.

Of the 308 patients included in the analysis, 66 patients (21.4%) had admission hyperglycemia. Severe admission hyperglycemia was present in 8 of the 66 patients (2.6% of all patients, 12.1% of patients with admission hyperglycemia). One patient was hypoglycemic at admission (glucose 3.1 mmol/l). Patients with admission hyperglycemia were older (mean age 45.6 versus 39.1 years, p=0.002) and less often female (60.6% versus 74.4%, p=0.03) compared to normoglycemic patients (Table 1). Coma at presentation was more common among patients with admission hyperglycemia (31.3% versus 5.0%, p<0.001), but other baseline clinical manifestations and risk factors did not differ between the 2 groups.

There were no statistically significant differences in the location of thrombosis between the groups. Patients with admission hyperglycemia more often had a brain parenchymal lesion (69.7% versus 55.8%, p=0.04), which was because of a higher frequency of intracerebral hemorrhagic lesions (53.0% versus 32.6%, p=0.002, Table 1). Patients with admission hyperglycemia were more often admitted to the intensive care unit (59.1% versus 23.6%, p<0.001), less often received anticoagulation (89.4% versus 97.9%, p=0.001), and more often underwent decompressive hemicraniectomy (19.7% versus 3.7%, p<0.001). Reasons for withholding anticoagulation were intracranial infection (n=4), chronic CVT (n=2), death before anticoagulation could be started (n=3), and traumatic CVT (n=2). At follow-up, 2 patients were diagnosed with diabetes mellitus, both of which had hyperglycemia on admission.

Scores on the mRS at follow-up were available for 296 patients (98% of patients with, and 95% of patients without admission hyperglycemia). For the 12 patients with missing mRS scores, we did have information on mortality status. The median duration of follow-up was 6 months in both groups. The mRS distribution is shown in Figure 2. Overall, patients with hyperglycemia had worse scores on the mRS than normoglycemic patients. Frequencies of mRS score of 3 to 6 (33.8% versus 10.4%, p<0.001) and mortality (21.2% versus 5.0%, p<0.001) were both higher in patients with admission hyperglycemia compared to those without admission hyperglycemia (Table 2). After adjustment of the pre-defined potential confounding variables, the risk of mRS score of 3 to 6 at last follow-up was increased in patients with admission hyperglycemia (adjusted odds ratio [OR], 3.10; 95% confidence interval [CI], 1.35-7.12). The risk of mortality was also higher in patients with admission hyperglycemia (adjusted OR, 4.13; 95% CI, 1.41-12.09). When included as a continuous variable, increased glucose concentration was associated with a higher risk of death or dependency (adjusted OR per 1 mmol/l increase in glucose concentration: 1.50; 95% CI, 1.21-1.86; p<0.001) and mortality (adjusted OR per 1 mmol/l increase in glucose concentration: 1.73; 95% CI, 1.30-2.31; p<0.001) at last follow-up. When we stratified by severity of admission hyperglycemia, we found that severe admission hyperglycemia was a stronger predictor for poor outcome than mild hyperglycemia (Table 3).

Compared to patients with normal admission glucose, those with severe admission hyperglycemia had a 33-fold higher risk of mortality at last follow-up (adjusted OR, 33.36; 95% CI, 3.87-287.28).

TABLE 3. Stratification by severity of admission hyperglycemia.

	Number of patients with outcome		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
mRS, 3-6	**mRS, 0-2**	**mRS, 3-6**		
≤7.7 mmol/l	202 (80.8%)	24 (52.2%)	1 *	1 *
7.8 – 11.0 mmol/l	46 (18.4%)	16 (34.8%)	2.93 (1.44-5.95)	2.32 (0.97-5.55)
≥11.1 mmol/l	2 (0.8%)	6 (13.0%)	25.25 (4.82-132.18)	11.59 (1.74-77.30)
Mortality	**Alive**	**Dead**		
≤7.7 mmol/l	225 (79.8%)	12 (46.2%)	1 *	1 *
7.8 – 11.0 mmol/l	54 (19.1%)	9 (34.6%)	3.13 (1.25-7.79)	3.16 (0.99-10.13)
≥11.1 mmol/l	3 (1.1%)	5 (19.2%)	31.25 (6.67-146.45)	33.36 (3.87-287.28)

*The multivariate model is adjusted for age, sex, coma, malignancy, infection, intracerebral hemorrhage, deep cerebral venous thrombosis, and location of recruitment. * Patients with a glucose concentration of ≤7.7 mmol/l were the reference category. mRS was not available for 12 patients (1 with admission hyperglycemia and 11 without admission hyperglycemia). CI indicates confidence interval; mRS, modified Rankin Scale; OR, odds ratio.*

DISCUSSION

This is the first study in which the association between admission glucose concentration and clinical outcome in patients with CVT is examined. Our data show that admission hyperglycemia is a strong and independent predictor for poor clinical outcome in CVT. This relation seems to be dose-dependent and in patients with severe admission hyperglycemia (glucose ≥11.1 mmol/l; ≥200 mg/dl), the risk of death or mRS score of 3 to 6 was substantially increased. Measurement of glucose concentration is inexpensive and is standard practice for patients with CVT, which makes our results easily translatable into daily practice. Admission hyperglycemia might be of use for risk stratification in CVT.

While our study shows a strong association between admission hyperglycemia and poor outcome in CVT, this finding does not necessarily imply a causal relationship. Elevated blood glucose might be a marker for the severity of brain injury in patients with CVT. In patients with aneurysmal subarachnoid hemorrhage, glucose concentration has been shown to be correlated with the magnitude of the hemorrhage.[12] Nevertheless, there are several arguments that are in favor of a causal relation between admission hyperglycemia and poor outcome in CVT. First, admission hyperglycemia increases the risk of developing thrombosis, as has been shown in patients who underwent orthopedic surgery.[18] Second, experimental studies

indicate that acute hyperglycemia causes hypercoagulability. For instance, hyperglycemia has been found to result in increased concentrations of thrombin-antithrombin complexes, factor VIII activity, and soluble tissue factor.[19] Third, an independent association between admission hyperglycemia and clinical outcome has been consistently shown in other conditions.[7, 12] Finally, our data show that there is a concentration-dependent effect in the association between admission hyperglycemia and poor outcome in CVT, and the presence of a concentration-response effect increases the likelihood of a causal relation.[20]

Several mechanisms have been proposed to explain why hyperglycemia increases the risk of poor outcome in stroke. Stroke results in a generalized stress reaction that involves activation of the hypothalamic-pituitary-adrenal axis. Activation of this pathway results in release of stress hormones which increase glucose concentration.[7, 11] A more severe stroke could lead to a stronger activation of this pathway and thus a higher glucose concentration. There is also evidence that suggests that in the presence of hyperglycemia, infarcted brain tissue is more prone to hemorrhagic transformation, probably because of disruption of the blood-brain barrier.[21] The higher rate of intracerebral hemorrhages among hyperglycemic patients in our cohort would be in line with that hypothesis, especially because there was no difference in frequency of nonhemorrhagic lesions between the groups. However, this mechanism cannot fully explain the association between poor outcome and hyperglycemia in CVT, because we adjusted for baseline intracerebral hemorrhages in our analyses. Other hypotheses are that increased glucose concentration is toxic to ischemic brain tissue, impairs recanalization and reperfusion, and increases reperfusion injury.[7, 11]

The presence of unrecognized diabetes mellitus has been suggested a confounding variable for the association between hyperglycemia and poor clinical outcome.[11, 22] The main reason for this is that most previous studies included elderly patients, in whom diabetes mellitus is common, and assessed diseases for which diabetes mellitus (or a disturbed glucose metabolism) is a known risk factor, such as ischemic stroke or myocardial infarction.[11, 22] Preexistent diabetes mellitus or previously unrecognized disturbances of glucose metabolism are unlikely to have been a confounder in our population. Unlike ischemic stroke and myocardial infarction, diabetes mellitus is not a risk factor for CVT. The young age of patients with CVT makes the presence of unrecognized diabetes mellitus also implausible. This notion is supported by the small number of patients who were excluded because of preexisting diabetes mellitus (3% of all patients) and the small proportion of patients who were diagnosed with diabetes mellitus during follow-up (0.6% of study cohort). Our study therefore provides robust evidence that the association between admission hyperglycemia and poor clinical outcome is independent of diabetes mellitus.

If a causal relation exists between increased admission glucose concentration and poor clinical outcome in CVT, lowering glucose concentration might improve the outcome of these patients. The efficacy of intensive glucose control has not been evaluated in CVT. In patients with critical illness, randomized trials have shown conflicting results, with some showing benefit[18, 23], and others harm[24, 25] of this intervention. Studies that evaluated intensive glucose control in patients with ischemic stroke have also failed to show an effect on clinical outcome.[7, 26] In some studies tight glycemic control was even associated with increased infarct size.[27, 28] However, controlling blood glucose seems to be difficult in patients with stroke compared with intensive care unit patients, because fewer nursing personnel are assigned to each patient, and oral intake of nutrients is often resumed in patients with stroke after an initial fasting period. Typically, an unpredictable nutritional absorption is seen in this postfasting period.[7]

Several limitations of our study warrant comment. First, we had to exclude 16% of patients because of missing admission glucose concentration. However, apart from the frequency of intracerebral hemorrhage, there were no differences between in- and excluded patients (Table I in the online-only Data Supplement) makes it unlikely that excluding these cases resulted in an important bias. Second, the study included data from both a prospective and retrospective database. To acknowledge this limitation, we have termed the entire study retrospective. Third, the glucose concentration was not measured at a standardized time point related to the ictus and time of admission. Fourth, in contrast to arterial stroke, the exact time of onset can be difficult to determine in patients with CVT. However, the fact that there was no difference in mode of onset (acute, subacute, or chronic) between hyperglycemic and normoglycemic patients would suggest that this aspect did not bias the results. Fifth, there is no generally accepted definition for admission hyperglycemia. On the basis of previous studies, we chose a cutoff value of 7.8 mmol/l (141 mg/dl), but as we found a clear concentration-response effect, it is not likely that the results would have been substantially different if we had used a different cutoff.

In conclusion, we have found that admission hyperglycemia on admission is a strong and concentration-dependent predictor for poor clinical outcome in patients with CVT without a history of diabetes mellitus. The strength of the association, the presence of a concentration-response effect, and the consistency with observations in other conditions, suggests a causal relation between admission hyperglycemia and poor outcome in these patients. The underlying pathophysiology of this association remains to be examined. Whether tight glucose control can improve the outcome of patients with CVT and admission hyperglycemia needs to be resolved in a randomized clinical trial.

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SUPPLEMENTAL TABLE I.   Comparison between included and excluded patients.

	Included (n=308)	Excluded (n=72)	P value
Demographics			
Female (%)	220/308 (71.4)	45/72 (62.5)	0.14
Mean age (SD)	40.5	40.8	0.88
Symptoms and signs			
Headache	259/305 (84.9)	60/70 (85.7)	0.67
Focal neurological deficit	187/304 (61.5)	45/71 (63.4)	0.67
Seizure(s)	97/305 (31.8)	20/72 (27.8)	0.51
Coma (GCS <9)	32/302 (10.6)	7/71 (9.9)	0.86
Papilledema	55/193 (28.5)	8/44 (18.2)	0.35
Risk factors			
Previous thrombosis	24/307 (7.8)	3/72 (4.2)	0.28
Genetic thrombophilia	35/270 (13.0)	7/60 (11.7)	0.82
Inflammatory bowel disease	12/308 (3.9)	1/72 (1.4)	0.29
Previous infection	54/302 (17.9)	16/71 (22.5)	0.37
Malignancy	21/307 (6.8)	9/71 (12.7)	0.10
Thrombotic medication	38/307 (12.4)	9/69 (13.0)	0.88
Thrombosed sinuses			
Superior sagittal sinus	177/308 (57.5)	43/72 (59.7)	0.73
Lateral sinus left	148/308 (48.1)	39/72 (54.2)	0.35
Lateral sinus right	132/308 (42.9)	33/72 (45.8)	0.65
Straight sinus	69/307 (22.5)	16/72 (22.2)	0.96
Parenchymal lesions			
Intracerebral hemorrhage or hemorrhagic infarct	114/308 (37.0)	15/72 (20.8)	0.009
Brain edema	97/308 (31.5)	23/72 (31.9)	0.94
Treatment			
Anticoagulation	296/308 (96.1)	22/23 (95.7)	0.98

SD indicates standard deviation; *GCS*, Glasgow Coma Scale.

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8

CLINICAL OUTCOME OF ANTICOAGULANT TREATMENT IN HEAD OR NECK INFECTION ASSOCIATED CEREBRAL VENOUS THROMBOSIS

Susanna M. Zuurbier, Jonathan M. Coutinho, Jan Stam, Patricia Canhão
Fernando Barinagarrementeria, Marie-Germaine Bousser, José M. Ferro

ABSTRACT

Background
Local infections of the head or neck are a cause of cerebral venous thrombosis. Treatment of infectious cerebral venous thrombosis with heparin is controversial. We examined whether this treatment was associated with intracranial hemorrhagic complications and poor clinical outcome.

Methods
We retrieved data from a prospective cohort study of 624 cerebral venous thrombosis patients. We compared patients with and without an infection of the head or neck and anticoagulated versus not anticoagulated. We examined death or dependency and new intracerebral hemorrhages.

Results
Six hundred four of 624 patients were eligible for the study. Fifty-seven patients had an infection of the head or neck (9.4%). Comparing data between infection and noninfection patients, the frequency of therapeutic doses of heparin was similar in both groups (82.5% versus 83.7%). New intracerebral hemorrhages were more common in patients with an infection (12.3% versus 5.3%, p=0.04), but death or dependency did not differ between patients with and without an infection (15.8% versus 13.7%). In patients with an infection of the head or neck, there was no significant difference in the frequency of new intracerebral hemorrhages and poor outcome between patients who did or did not receive therapeutic doses of heparin.

Conclusion
New intracerebral hemorrhages were more frequent in patients with an infection. The use of therapeutic doses of heparin did not seem to influence the risk of new intracranial hemorrhages or poor clinical outcome, but the number of patients who did not receive anticoagulation was too small to draw firm conclusions about safety of heparin in adults with cerebral venous thrombosis and an infection of the head or neck.

INTRODUCTION

Local infections of the head or neck can cause cerebral venous thrombosis (CVT).[1, 2] Common examples include ear infections that propagate to the lateral sinuses, cutaneous facial infections that spread to the cavernous sinus, and intracranial infections, such as meningitis and empyema. In older studies ≈20% to 60% of patients with CVT had an associated infection of the head or neck,[3–7] but recent publications show that this proportion has decreased to ≈6% to12% in the developed world,[1, 8] probably because of improved antibiotic treatment.

On the basis of limited data from randomized trials, heparin has been the primary therapy for patients with CVT.[9–14] Patients with an infection of the head or neck, however, were not included in these trials, and it is unknown whether this recommendation should apply to these patients. Limited data suggest that anticoagulant therapy in patients with meningitis is associated with a higher rate of intracerebral hemorrhagic complications[15] and increased mortality.[16] With the exception of case reports,[17, 18] there are no data on the use of heparin in patients with CVT and a concurrent infection. International guidelines for CVT also do not provide a separate recommendation on the use of heparin in this subgroup.[13, 14]

The International Study on Cerebral Venous and dural sinus Thrombosis (ISCVT) is the largest prospective cohort study on adult CVT.[19] In the current study, we have analyzed patients from this cohort who had a concurrent infection of the head or neck. Specific aims were to determine how often these patients were treated with therapeutic doses of heparin and whether the use of heparin was associated with intracranial hemorrhagic complications and poor clinical outcome.

METHODS

Study design and patient selection
The organization of the ISCVT has been described previously. Briefly, ISCVT was a prospective international observational cohort study that included 624 consecutive adult patients with symptomatic CVT between 1998 and 2001.[19] Extensive information on baseline clinical characteristics, radiological findings, treatment, and complications during admission were recorded on a standardized case record form. A list of potential risk factors was attached to the case record form, including different types of infections: regional infections (meningitis or other central nervous system (CNS) infections, infections of parameningeal neighboring structures (cranial skin, and ear, nose, and throat (ENT)), and generalized or distant infections (HIV infection or other systemic infections). For the current study, we identified all patients with an infection of the head or neck, defined by the presence of an ENT, faciocranial skin, or central nervous system (CNS) infection. The diagnosis of ENT infection and

their types were established by local investigators. CNS infection was confirmed by culture of cerebrospinal fluid or explorative surgery. We excluded patients with infections at other locations because a causal relation between distant infections and CVT is unclear.

Neuro-imaging

CVT was confirmed by magnetic resonance venography, computed tomographic venography, conventional angiography, surgery, or autopsy. At baseline, all patients received computed tomographic or magnetic resonance imaging. Repeated cerebral imaging was performed at the discretion of the treating physician, and documentation of new parenchymal lesions (symptomatic or not) was required. We classified intracerebral lesions as nonhemorrhagic lesion (focal oedema or venous infarct without signs of hemorrhage) and intracerebral hemorrhage (ICH; hemorrhagic infarct or ICH). There was no central reading committee of computed tomography or magnetic resonance imaging or validation of the reports of the local investigators. The decision to treat the patient with heparin was left to the local investigator. The dose (prophylactic or therapeutic)[20] and type of heparin were registered, and monitoring of anticoagulant therapy was performed according to local hospital protocol. Complications, such as seizures and their types, were established by local neurologists.

Endpoints

We considered death or dependency (defined as a modified Rankin Scale, >2) at last follow-up as the primary outcome. Secondary end points were all-cause mortality at 30 days (the different causes of death were recorded on a case record form),[21] complete recovery (modified Rankin Scale, 0 or 1) at last follow-up, neurological worsening, and the occurrence of a new ICH after diagnosis. Systemic hemorrhages were not recorded but blood transfusions or any surgery were registered.

Statistical analysis

We first compared patients with an infection of the head or neck with those without an infection. We then compared patients with an infection of the head or neck treated with heparin treatment in therapeutic dosages to those who did not receive heparin or who received heparin only in prophylactic dose.

For comparison of continuous data, we used a Student t or a Mann–Whitney U test and for categorical data a χ^2 or Fisher exact test, whichever was appropriate. We provide continuous data as a mean with SD, or, if the data did not have a normal distribution, as a median with interquartile range. Categorical variables are given as the number of patients in which the variable was present and the total number of patients for which that variable was reported. P values of <0.05 were considered statistically significant. All data were analyzed with SPSS version 21 (IBM Inc., Armonk, NY).
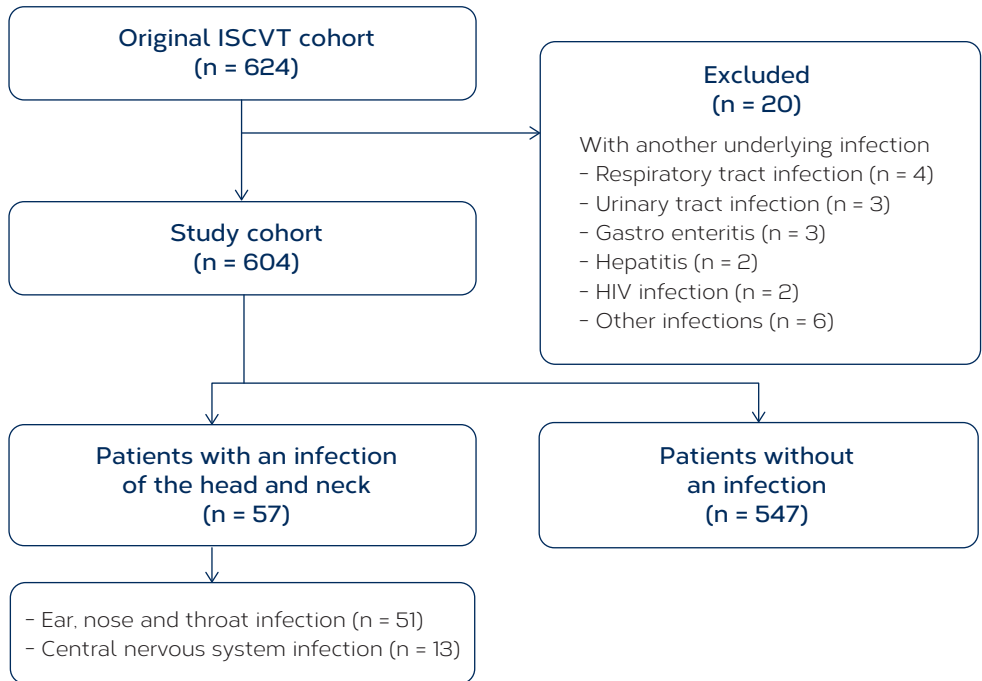
FIGURE 1.   Flowchart of the study selection.

RESULTS

Of the 624 patients in the ISCVT, 77 patients had an infection (12.3%). Twenty of these had an infection outside the head or neck region (respiratory tract (n=4), urinary tract (n=3), gastroenteritis (n=3), hepatitis (n=2), HIV infection (n=2), and other (n=6)), and these patients were excluded. Therefore, our study cohort consisted of 57 patients with a head or neck infection and 547 patients without an infection (Figure 1).

Type of infection
Of the 57 patients with CVT and an infection of the head or neck, 51 patients (89.5%) had an ENT infection. The exact type of ENT infection was specified in 29 patients: otitis/mastoiditis (n=18), sinusitis (n=9), pharyngitis (n=1), and tonsillitis (n=1). Thirteen of 57 patients (22.8%) had a CNS infection, confirmed by cerebrospinal fluid culture (n=12) or surgery (n=1). Seven patients had both an ENT and CNS infection (12.3%). Seven patients had a distant infection in addition to the regional infection: HIV infection (3), gastroenteritis (2), sepsis (1), and endocarditis (1).

TABLE 1. Baseline characteristics.

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	Infection of the head or neck (n=57)	No infection (n=547)	P value
Demographics			
Women	34/57 (59.6)	421/547 (77.0)	0.004
Median age (IQR)	34.0 (24-48)	37.0 (27-50)	0.30
Symptoms and signs			
Headache	51/57 (89.5)	486/546 (89.0)	0.92
Paresis	17/57 (29.8)	210/547 (38.4)	0.20
Seizure(s)	19/57 (33.3)	223/547 (40.8)	0.28
Coma (GCS score <9)	5/53 (9.4)	26/527 (4.9)	0.17
Mental status disorder	10/57 (17.5)	121/547 (22.1)	0.43
Papilledema	26/55 (47.3)	145/539 (26.9)	0.001
Diplopia	15/57 (26.3)	67/547 (12.2)	0.003
Isolated intracranial hypertension	13/57 (22.8)	101/547 (18.5)	0.43
Day symptom onset, admission, median (IQR)	6 (2-13)	4 (2-11)	0.63
Day symptom onset, diagnosis, median (IQR)	9 (4-19)	7 (3-16)	0.66
Risk factors			
Acquired thrombophilia *	10/57 (17.5)	87/547 (15.9)	0.75
Malignancy	1/57 (1.8)	42/547 (7.7)	0.10
Oral contraceptives †	10/34 (29.4)	197/421 (46.8)	0.05
Pregnancy or puerperium †	4/34 (11.8)	73/421 (17.3)	0.41
Additional risk factor identified	33/57 (57.9)	–	NA
Thrombosed sinuses/veins			
Superior sagittal sinus	35/57 (61.4)	340/546 (62.3)	0.90
Lateral sinus left	26/57 (45.6)	242/546 (44.3)	0.85
Lateral sinus right	25/57 (43.9)	222/546 (40.7)	0.64
Straight sinus	4/57 (7.0)	101/546 (18.5)	0.03
Cavernous sinus	4/57 (7.0)	4/546 (0.7)	<0.001
Parenchymal lesions			
Any parenchymal lesion	25/57 (43.9)	353/546 (64.7)	0.002
Nonhemorrhagic lesion	13/57 (22.8)	126/546 (23.1)	0.96
Intracerebral hemorrhage	12/57 (21.1)	227/546 (41.6)	0.003
Therapy			
Therapeutic dose heparin	47/57 (82.5)	458/547 (83.7)	0.81
Low-molecular weight heparin	25/57 (43.9)	187/547 (34.2)	0.15

	Infection of the head or neck (n=57)	No infection (n=547)	P value
Therapy (contintued)			
Unfractionated heparin	31/57 (54.4)	360/547 (65.8)	0.09
Prophylactic dose heparin	4/57 (7.0)	18/547 (3.3)	0.15
Day diagnosis, start of heparin, median (IQR)	0 (0-1)	0 (0-1)	0.63
ENT surgery (%)	5/57 (8.8)	0/547 (0.0)	–
Neurosurgery (%)	1/57 (1.8)	16/547 (2.9)	0.57
Oral anticoagulantion (%)	38/57 (66.7)	402/547 (73.5)	0.27

* Homocysteinemia, antiphospholipid antibody, and previous venous thrombosis. † Women only.

ENT indicates ear, nose, and throat; NA, not applicable. GCS, Glasgow Coma Scale; IQR, interquartile range.

TABLE 2. Complications and outcome.

	Infection of the head or neck (n=57)	No infection (n=547)	P value
Neurological worsening	16/57 (28.1)	131/547 (23.9)	0.49
Day diagnosis, deterioration, median (IQR)	4 (1-11)	2 (0-6)	0.97
Type of clinical worsening			
Decreased consciousness *	8/57 (14.0)	73/547 (13.3)	0.89
Altered mental status †	4/57 (7.0)	39/547 (7.1)	0.98
Focal deficit	7/57 (12.3)	35/547 (6.4)	0.10
Seizure	4/57 (7.0)	45/547 (8.2)	0.75
Repeated imaging ‡	27/57 (47.4)	238 /545 (43.7)	0.59
Any new parenchymal lesion	8/57 (14.0)	48/545 (8.8)	0.20
New nonhemorrhagic lesion	1/57 (1.8)	19/545 (3.5)	0.90
New intracerebral hemorrhage	7/57 (12.3)	29/545 (5.3)	0.04
Outcome			
mRS score, 0-1	46/57 (80.7)	431/547 (78.8)	0.74
mRS score, 3-6	9/57 (15.8)	75/547 (13.7)	0.67
Mortality at 30 d	3/57 (5.3)	18/547 (3.3)	0.44

* Defined as Glasgow Coma Scale on admission <15 (stupor, 14-9; coma, <9). † Includes executive deficits (frontal lobe syndromes), delirium and personality or other acute behavioural changes but not distur-bances of the instrumental cognitive domains, such as aphasia, apraxia, agnosia, amnesia or visuospatial disturbances. ‡ Patients who did not receive repeated imaging were scored as no new parenchymal lesions. IQR indicates interquartile range; mRS, modified Rankin Scale.

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Baseline characteristics
Baseline characteristics of the 57 patients with a head or neck infection are shown in Table 1. Patients with a head or neck infection less often were women (59.6% versus 77.0%, p=0.004), and more often had papilledema (47.3% versus 26.9%, p= 0.001) and diplopia (26.3% versus 12.2%, p=0.003) compared with patients without an infection. About 57.9% of patients with an infection had an additional risk factor. Thrombosis of the cavernous sinus occurred more frequently in patients with an infection (7.0% versus 0.7%, p<0.001). An ICH at baseline was less common in patients with an infection (21.1% versus 41.6%, p=0.003). All patients with an infec- tion and ICH at baseline had an ENT infection, and none had a CNS infection. Seven of 13 patients with a CNS infection (53.8%) had a nonhemorrhagic lesion at baseline compared with 6 of 44 patients with an ENT infection (13.6%). The proportion of patients who received heparin in therapeutic doses did not differ between patients with and without an infection (82.5% versus 83.7%).

Complications during admission
A quarter of the patients in each group deteriorated neurologically during admis- sion (Table 2). A new ICH occurred more often in patients with an infection of the head or neck compared to those without an infection (7/57, 12.3% versus 29/545, 5.3%, p=0.04). When specified by type of infection, 3/13 patients (23.1%) with a CNS infection developed a new ICH, compared to 4/44 patients (9.1%) with an ENT infection. There was no statistically significant difference in the frequency of new non-hemorrhagic lesions between patients with an infection of the head or neck and those without an infection.

Clinical outcome
Nine patients (15.8%) with an infection of the head or neck were dead or dependent (mRS >2) at last follow-up, compared to 75 patients (13.7%) without an infection (Table 2). Death or dependency was especially high in patients with a CNS infection (4/13, 30.8%). Mortality did not differ significantly between the groups (5.3% versus 3.3%, p=0.44). In total, 21 patients died. In 16/18 patients without an infection who had died, death was due to cerebral herniation and therefore directly related to CVT. In the other 2 patients the cause of dead was not reported. In patients with an infection of the head or neck, death due to cerebral herniation occurred in 1/3 patients. In the two other patients death was not directly related to CVT (one due to HIV infection, and due to endocarditis). The full distribution of the mRS at last follow-up in each group is shown in Figure I in the Online-only Data Supplement. The median time to last follow-up was 476 days (IQR 332–760 days).

Heparin in patients with an infection of the head or neck
Forty-seven of 57 patients (82.5%) with an infection received therapeutic doses of heparin in the acute phase. Of the remaining 10 patients 4 received prophylactic doses of heparin and 6 received no heparin. There were no major differences in

demographics, clinical manifestations, or baseline radiological findings between patients who did or did not receive therapeutic dose of heparin (Table I in the Online-only Data Supplement). Clinical deterioration occurred more often in patients treated with heparin (31.9% versus 10.0%, p=0.17, Table 3), but there was no difference in the frequency of new parenchymal lesions. All patients with a new ICH were treated with therapeutic dose of heparin, with the exception of 2 patients without an infection of the head or neck, and 1 patient with a CNS infection and endocarditis. Clinical outcome at follow-up did not differ between patients who did or did not receive therapeutic dose of heparin.

TABLE 3. Comparison of characteristics in cerebral venous thrombosis patients and an infection of the head or neck, with and without therapeutic dose of heparin treatment.

	Heparin treatment (n=47)	No heparin treatment (n=10)	P value
Neurological worsening	15/47 (31.9)	1/10 (10.0)	0.17
Type of neurological worsening			
Decreased consciousness *	7/47 (14.9)	1/10 (10)	0.69
Altered mental status †	4/47 (8.5)	0/10 (0)	0.35
Focal deficit	7/47 (14.9)	0/10 (0)	0.42
Seizure	4/47 (8.5)	0/10 (0)	0.35
Visual loss	2/47 (4.3)	0/10 (0)	0.52
Other (headache/diplopia)	4/47 (8.5)	0/10 (0)	0.35
Repeated imaging ‡	23/47 (48.9)	4/10 (40.0)	0.62
Any new parenchymal lesion	7/23 (30.4)	1/4 (25.0)	0.67
New nonhemorrhagic lesion	1/23 (4.3)	0/4 (0.0)	–
New intracerebral hemorrhage	6/23 (26.1)	1/4 (25.0)	0.97
Outcome			
mRS score, 0-1	39/47 (83.0)	7/10 (70.0)	0.35
mRS score, 3-6	6/47 (12.8)	3/10 (30.0)	0.18
Mortality 30 d	2/47 (4.3)	1/10 (10.0)	0.47

* Defined as Glasgow Coma Scale on admission <15 (stupor, 14-9; coma, <9). † Includes executive deficits (frontal lobe syndromes), delirium and personality or other acute behavioural changes but not disturbances of the instrumental cognitive domains, such as aphasia, apraxia, agnosia, amnesia or visuospatial disturbances. ‡ Patients who did not receive repeated imaging were scored as no new parenchymal lesions. mRS indicates modified Rankin Scale.

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DISCUSSION

Our data indicate that a local infection nowadays is an uncommon cause of CVT in adults. The frequency of an infection as a risk factor is similar to what was reported in another recent cohort study.[22] Even in developing countries, the reported fraction of a local infection in adults with CVT is only 15%.[23] One outlier is large retrospective study from the United States based on administrative data which found that more than 80% of CVT cases were "pyogenic".[24] The over representation of pyogenic CVT in this study could be due to an underreporting of non-pyogenic CVT, or – more likely – to an erroneous code for CVT: the diagnosis of CVT was drawn from a national database.[24] Patients with an infection of the head or neck more often had papilledema and diplopia at presentation, and less often an ICH. This would suggest these patients more often had intracranial hypertension due to occlusion of a large sinus, and less often occlusion of a cortical vein. Even if we omit the cases with cavernous sinus thrombosis, which are usually septic, the differences in papilledema and ICH were still significant.

An important observation is that a new ICH occurred more often in patients with an infection of the head or neck (12.3% versus 5.3%), despite the fact that a baseline ICH was less common in these patients. The increased risk of new ICH in patients with an infection of the head or neck is especially related to the increased risk of new ICH in patients with a CNS infection. Three out of 13 patients (23.1%) with a CNS infection developed a new ICH. One of them was not treated with therapeutic dose of heparin, and had additionally an endocarditis. In patients with an ENT infection, 4 out of 44 patients (9.1%) developed a new ICH during hospitalization, which is closer to the incidence of new ICH in patients without an infection (5.3%). Remarkable, we found that patients with a CNS infection had a higher rate of non-hemorrhagic infarcts at baseline imaging, compared to patients with an ENT infection (53.8% versus 13.6% respectively). The underlying pathophysiology of the higher frequency of new ICH, especially in patients with a CNS infection, is unknown, but could be related due to the extension of the thrombus to the cortical veins. A pathophysiological mechanism may be that there is a dysregulation of both the coagulation and fibrinolytic pathways. The massive clotting may result in the local depletion of coagulation factors, which together with microvascular damage, vasculitis, and cerebral infarction, might lead to the increased risk of ICH.[25]

The proportion of patients with CVT and an infection treated with therapeutic dose of heparin (82.5%) is similar to that of the entire ISCVT cohort (83.3%).[26] Apparently most neurologists believe that heparin is indicated and safe in these patients, although there is no evidence from randomized trials for the use of heparin in patients with a septic CVT. The use of therapeutic dose of heparin did not appear to influence the risk of new ICH in our study, but the number of patients who did not receive anticoagulation was too small to draw firm conclusions. Interestingly,

clinical deterioration occurred three times more often in patients treated with therapeutic dose of heparin (31.9% versus 10.0%), but these data should be interpreted with caution because of the small numbers and the fact that this analysis was not adjusted for potential confounders. The causes for the clinical deterioration of the patients with an infection of the head or neck who received therapeutic dose of heparin are not completely understood, and may need clarification in further studies. Uncertainty about the use of therapeutic dose of heparin remains especially for the group of patients with a CNS infection, because the small number of patients, and since there are data that suggest that these patients have a higher risk of hemorrhage if treated with anticoagulation.[27] The results of our study cannot be extrapolated to pediatric patients with CVT, because the ISCVT included only adult patients. A previous study indicates that treatment with therapeutic doses of heparin was not associated with serious hemorrhages in selected pediatric patients with CVT.[28]

Our study has several limitations. First, we could only include a limited number of patients with an infection of the head or neck, and only 13 patients with an underlying CNS infection. Second, infections of the head or neck were categorised as diagnosed by the clinician and not judged by an adjudication committee, according to predefined diagnostic criteria. Another limitation is the lack of central reading of the imaging results and the fact that repeat imaging was not performed in all patients. In addition, no difference could be made between symptomatic and asymptomatic new parenchymal lesions. Because this is an observational study, and the ISCVT was not designed to this specific analysis, our data cannot be used for strong treatment recommendations. Although both groups were comparable regarding most baseline characteristics, we cannot exclude the risk of bias. Adjusting for prognostic factors was impossible because the group of patients with an infection of the head or neck was too small.

In conclusion, the ISCVT data show that treatment with therapeutic doses of heparin is frequently given to adults with cerebral venous thrombosis and an infection of the head or neck. Although the potential benefit of therapeutic doses of heparin in adults with cerebral venous thrombosis and an infection of the head or neck cannot be determined with confidence from the ISCVT data, the results of our study suggest that the use of heparin did not appear to influence this risk of new intracerebral hemorrhages or of bad outcome, but the number of patients who did not receive anticoagulation was too small to draw firm conclusions about safety of heparin in adults with cerebral venous thrombosis and an infection of the head or neck.

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SUPPLEMENTAL TABLE I. Comparison of characteristics in CVT patients and an infection of the head or neck, with and without heparin treatment.

	Heparin treatment (n=47)	No heparin treatment (n=10)	P value
Demographic findings			
Female (%)	26/47 (55.3)	8/10 (80.0)	0.15
Age (median, IQR)	34 (25-46)	34 (21-51)	0.96
Symptoms and signs			
Headache	42/47 (89.4)	9/10 (90.0)	0.95
Paresis	12/47 (25.5)	5/10 (50.0)	0.13
Seizure(s)	14/47 (29.8)	5/10 (50.0)	0.23
Coma (GCS <9)	4/43 (9.3)	1/10 (10.0)	0.95
Mental status disorder	8/47 (17.0)	2/10 (20.0)	0.83
Papilledema	20/45 (44.4)	6/10 (60.0)	0.38
Diplopia	11/47 (23.4)	4/10 (40.0)	0.29
Isolated intracranial hypertension	12/47 (25.5)	1/10 (10.0)	0.30
Radiological findings			
Thrombosed sinuses/veins			
Superior sagittal sinus	28/47 (59.6)	7/10 (70.0)	0.55
Lateral sinus left and/or right	34/47 (72.3)	6/10 (60.0)	0.63
Straight sinus	2/47 (4.3)	1/10 (10.0)	0.08
Deep cerebral venous system *	1/47 (2.1)	1/10 (10.0)	0.23
Cortical vein	6/47 (12.8)	0/10 (0.0)	0.81
Cavernous sinus	3/47 (6.4)	2/10 (20.0)	0.69
Parenchymal lesions			
Any parenchymal lesion	20/47 (42.6)	5/10 (50.0)	0.67
Non hemorrhagic lesion	9/47 (19.1)	4/10 (40.0)	0.16
Intracerebral hemorrhage	11/47 (23.4)	1/10 (10.0)	0.35

* Thrombosis in one or more of the following veins: internal cerebral veins, vein of Galen, and basal vein of Rosenthal. IQR indicates inter quartile range; GCS, Glasgow Coma Scale.
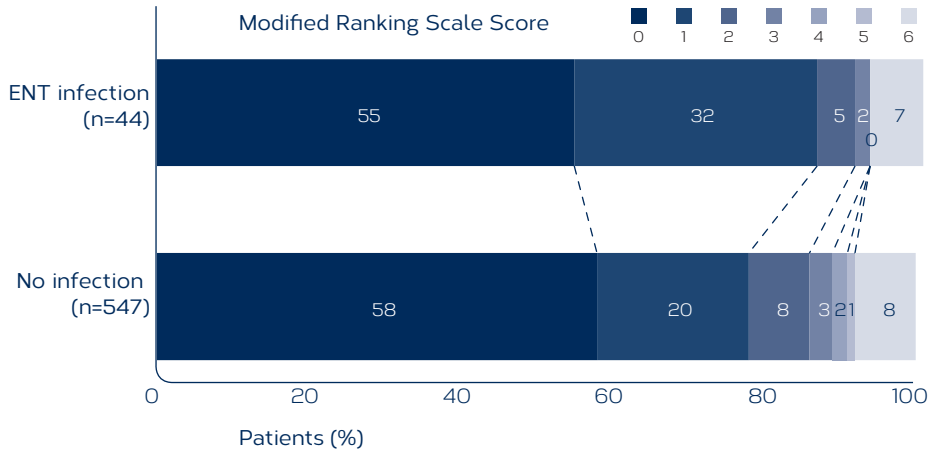
SUPPLEMENTAL FIGURE IA. Modified Rankin Scale Score of patients with an underlying ENT infection.
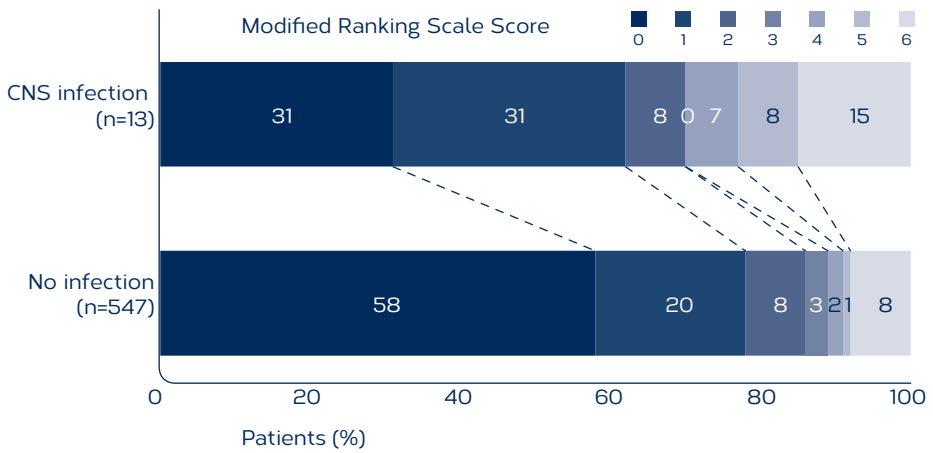
SUPPLEMENTAL FIGURE IB. Modified Rankin Scale Score of patients with an underlying CNS infection.

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HYDROCEPHALUS IN CEREBRAL VENOUS THROMBOSIS

Susanna M. Zuurbier, René van den Berg, Dirk Troost, Charles B. Majoie, Jan Stam, Jonathan M. Coutinho

ABSTRACT

Background

Increased intracranial pressure is common in cerebral venous thrombosis (CVT), but hydrocephalus is rarely reported in these patients.

Methods

We examined the frequency, pathophysiology and associated clinical manifestations of hydrocephalus in patients with CVT admitted to our hospital between 2000 and 2010 (prospectively since July 2006). Hydrocephalus was defined as a bicaudate index larger than the 95th percentile for age, and/or a radial width of the temporal horn of >5 mm. We excluded patients in whom hydrocephalus was caused by a disease other than CVT or if it was iatrogenic.

Results

20 out of 99 patients with CVT had hydrocephalus. 6 patients with hydrocephalus were excluded from the analysis. Patients with hydrocephalus more often had focal neurological deficits (86% versus 49%, p=0.02) and were more frequently comatose (43% versus 16%, p=0.03), as compared to patients without hydrocephalus. Deep cerebral venous thrombosis (64% versus 9%, p<0.001) and edema of the basal ganglia and thalami (64% versus 4%, p<0.001) were more common in patients with hydrocephalus. Intraventricular hemorrhage was present in 1 patient with hydrocephalus, compared to none among patients without hydrocephalus (7% versus 0%, p=0.15). Outcome at follow up was worse in patients with hydrocephalus (mRS 0-1, 36% versus 68%, p=0.02; mortality 29% versus 9%, p=0.07).

Conclusions

Hydrocephalus occurs more frequently in cerebral venous thrombosis than previously believed, especially in patients with deep cerebral venous thrombosis and edema of the basal ganglia. The presence of hydrocephalus is associated with a worse clinical outcome, but a direct causal relation is unlikely. Routine shunting procedures are not advisable.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare form of stroke with an estimated incidence of 1.3 per 100.000 among adults.[1] Thrombosis of the sinuses leads to impairment of cerebral spinal fluid drainage and venous outflow, which often causes increased intracranial pressure, with symptoms such as headache, papilledema and 6th nerve palsy.[2-4] Hydrocephalus, however, is rarely reported in patients with CVT and few studies have investigated this complication. Cohort studies of CVT reported incidences of hydrocephalus between 0.2% and 6.6%.[5-7] However, hydrocephalus was not a major research topic in any of these studies and specific definitions or details are not provided. All studies also lacked central review of imaging data and the validity of the estimates provided by these studies is therefore questionable. In fact, the only detailed reports on hydrocephalus in patients with CVT are case reports.[8-12] The aim of the present study was to systematically examine the incidence, risk factors, pathophysiology, associated clinical manifestations, and outcome of hydrocephalus in a large cohort of consecutive patients with CVT.

MATERIAL AND METHODS

Study population

We included consecutive patients with CVT aged 12 and older admitted to the Academic Medical Centre (University of Amsterdam) between January 1st 2000 and January 1st 2011. Our hospital serves as a tertiary referral center for CVT cases in the Netherlands. Since July 2006, all patients with CVT are enrolled in a prospective database, as described previously.[13] We retrospectively identified patients admitted between January 1st 2000 and June 30th 2006, using the International Classification of Diseases, 9th revision and the Dutch financial coding system for hospital care.[1] CVT was confirmed in all patients by one of the following: magnetic resonance imaging (MRI) with MRI-venography, computed tomographic-venography (CT-V), conventional angiography, or autopsy. We collected data on demographics, baseline clinical characteristics, and treatment. Clinical outcome was classified according to the modified Rankin Scale (mRS), a 7 point scale which ranges from 0 (complete recovery) to 6 (dead). We defined good outcome as a mRS score of 0 or 1 at last follow-up. Patients admitted before July 2006 for whom no mRS had been recorded were contacted by telephone to determine the score by means of a structured interview.[14] Under Dutch law, ethical approval did not have to be obtained for this observational study.

Imaging data and definition of hydrocephalus

All cerebral imaging results were re-evaluated by two neuroradiologists (RvdB and CBM). The type of scan, location of the thrombosis, presence and type of intracranial lesions, and the presence of hydrocephalus were documented. We determined the

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presence of hydrocephalus by measuring the bicaudate index (BCI) and the radial width of the temporal horn (rWTH), as described previously.[15, 16] Briefly, the BCI is the width of the frontal horns at the level of the caudate nuclei and the foramen of Monro divided by the corresponding width of the brain at the same level. To calculate age-adjusted relative sizes, the BCIs were divided by the corresponding upper limit (95th percentile) per age group, as previously reported.[16]

The rWTH of the lateral ventricle was measured at the tip of the temporal horn on (axial) imaging using the method described by Frisoni et al.[15] The rWTH was measured at the image slice where the temporal horn was the widest. Two parallel lines were drawn tangential to the margins of the temporal horn at its widest point. The rWTH is the distance between the two lines. Because control values for the rWTH have not been published, we measured the rWTH in a control group of healthy adults. For each patient with CVT, we selected an age-matched control patient who underwent cranial CT imaging because of a minor head injury between 2010 and 2012. Only patients without neurological co-morbidity and in whom the CT scan was unremarkable (without any traumatic injuries) were eligible as controls.

We defined hydrocephalus as one of the following a BCI above the 95th percentile for age, and/or a rWTH (uni- or bilateral) 2.5 standard deviations or more above the mean rWTH of the control group. Presence of hydrocephalus was determined on baseline imaging and on follow-up scans performed within 30 days of diagnosis. If a patient had hydrocephalus on multiple examinations, we used the scan in which the hydrocephalus was most severe. We excluded patients in whom hydrocephalus was caused by a disease other than CVT or if it was deemed iatrogenic (e.g. following decompressive hemicraniectomy).

Statistical analysis

For categorical variables we used the Pearson χ^2 or Fisher's exact test if appropriate. The Student's t test or Mann-Whitney test (for skewed distributions) were used for continuous variables. To determine whether hydrocephalus was associated with outcome, we performed multivariate logistic regression analysis. All analyses were performed with SPSS software, version 19.0.

RESULTS

The mean rWTH in the age-matched control group (no CVT) was 1.8 mm with a standard deviation of 1.2 mm. Therefore, the upper limit of normal for the rWTH was defined as 5 mm.

During the study period, 99 patients with CVT older than 12 were admitted, of whom 59 after July 2006 (prospective cohort). Twenty of these patients (20%) had
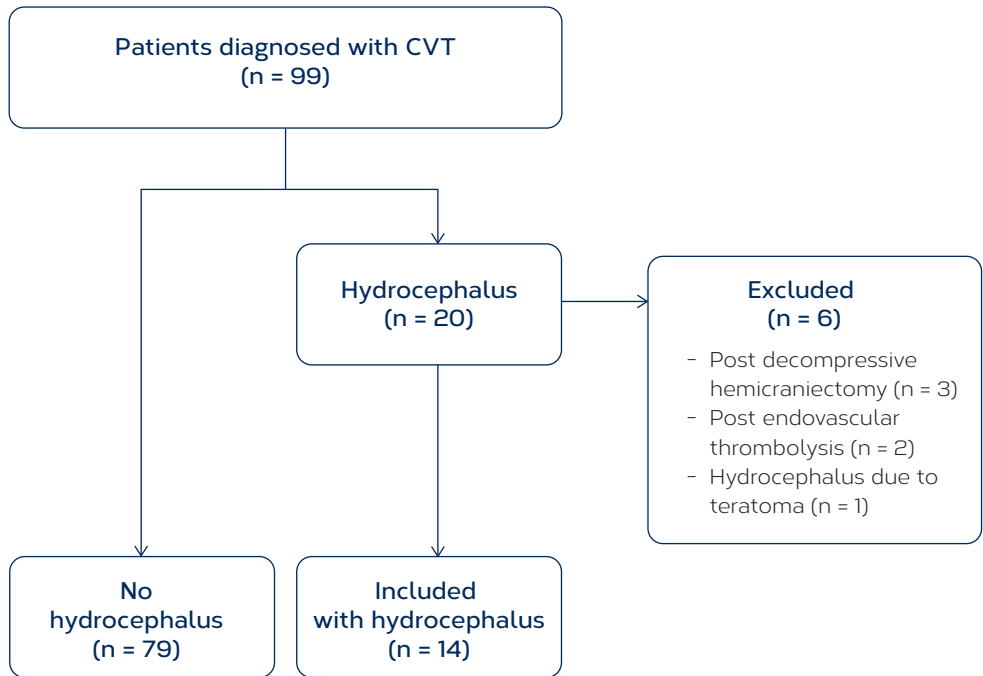
FIGURE 1. Flowchart of patient selection.

hydrocephalus (Figure 1). Six patients were excluded from the analysis because the hydrocephalus was iatrogenic or had another cause [after decompressive hemicraniectomy (3); complication of endovascular thrombolysis (2) and hydrocephalus due to a teratoma (1)]. Therefore, the study cohort consisted of 14 patients with and 79 patients without hydrocephalus. In 10 of 14 patients (71%) hydrocephalus was present at baseline. In the remaining patients hydrocephalus was found within 24 h of diagnosis (3 patients) or 8 days after diagnosis (1 patient). Thirteen patients (93%) had an increased rWTH (bilateral in 8) and only 2 (14%) had an increased BCI (Table 1). One patient had both an increased BCI and rWTH. The mean rWTH was 6.5 mm in the patients with hydrocephalus, compared to 2.1 mm in those without hydrocephalus. At baseline, patients with hydrocephalus more often had focal neurological deficits (86% versus 49%, p=0.02), fixed and dilated pupil(s) (14% versus1%, p=0.06), and a lower Glasgow Coma Scale (median 10 versus 15, p=0.01) as compared to patients without hydrocephalus. Other baseline clinical characteristics did not differ significantly. Lumbar puncture was performed in four patients with hydrocephalus, and all had an increased cerebrospinal fluid pressure (>20 cmH2O). In patients without hydrocephalus, ten patients underwent lumbar puncture and eight had an increased pressure.

TABLE 1. Baseline characteristics.

	Hydrocephalus (n=14)	No hydrocephalus (n=79)	P value
Hydrocephalus details			
Increased rWTH	13/14 (93)	–	NA
Bilateral	8/14 (57)	–	NA
Mean rWTH (mm, SD)	6.5 (1.8)	2.1 (1.4)	NA
Increased BCI	2/14 (14)	–	NA
Mean BCI (SD)	0.13 (0.04)	0.11 (0.03)	NA
Hydrocephalus at baseline	10/14 (71)	–	NA
Demographics			
Female	13/14 (93)	53/79 (67)	0.06
Mean age (SD)	33 (16)	37 (13)	>0.1
Symptoms and signs			
Duration symptom onset to diagnosis (days, median, IQR)	5 (2-12)	4 (2-7)	>0.1
Duration admission to diagnosis (days, median, IQR)	0 (0-1)	1 (0-2)	>0.1
Headache	13/14 (93)	67/79 (85)	>0.1
Focal neurological deficit	12/14 (86)	38/77 (49)	0.02
Seizure(s)	3/14 (21)	27/79 (34)	>0.1
Glasgow coma scale (median, IQR)	10 (8-14)	15 (11-15)	0.01
Coma	6/14 (43)	12/73 (16)	0.06
Fixed and dilated pupil(s)	2/14 (14)	1/79 (1)	0.06

rWTH indicates radial width of the temporal horn; BCI, bicaudate index; SD, standard deviation; IQR, inter-quartile range.

Patients with hydrocephalus more often had thrombosis of the straight sinus (64% versus 23%, p=0.002) and deep cerebral venous thrombosis (DCVT: internal cerebral veins, vein of Galen, and/or the basal vein of Rosenthal; 64% versus 9%, p<0.001, Table 2). In contrast, the superior sagittal sinus was less often involved in patients with hydrocephalus (21% versus 67%, p=0.001). Hypodensity of the basal ganglia and/or thalami on CT, suggesting edema, was present in 9/14 (64%) patients with hydrocephalus, as compared to 3/79 (4%) in those without hydrocephalus (p<0.001). In two of these nine patients, the presence of edema was confirmed with MRI. There was no difference in frequency of baseline intracerebral hemorrhages between the two groups (50% versus 54%). One patient with hydrocephalus had both supra- en

TABLE 2. Radiological findings, treatment and outcome.

	Hydrocephalus (n=14)	No hydrocephalus (n=79)	P value
Thrombosed sinuses			
Superior sagittal sinus	3/14 (21)	53/79 (67)	0.001
Lateral sinus (left and/or right)	12/14 (86)	59/79 (75)	>0.1
Straight sinus	9/14 (64)	18/79 (23)	0.002
Deep cerebral venous system *	9/14 (64)	7/79 (9)	<0.001
Thrombosis >1 sinus	13/14 (93)	67/79 (85)	>0.1
Parenchymal lesions			
Edema basal gangli/thalami †	9/14 (64)	3/79 (4)	<0.001
Intracerebral hemorrhagic lesion	7/14 (50)	43/79 (54)	>0.1
Intraventricular hemorrhage	1/14 (7)	0/79 (0)	0.15
Treatment			
Heparin treatment	13/14 (93)	79/79 (100)	>0.1
Endovascular treatment	9/14 (64)	14/78 (18)	<0.001
Decompressive hemicraniectomy	3/14 (21)	6/78 (8)	>0.1
Ventricular shunting procedure	1/14 (7)	2/79 (3)	>0.1
Clinical outcome at last follow-up)			
Duration of follow-up (median months, IQR)	16 (2-75)	8 (4-24)	>0.1
mRS 0-1 (recovery without handicap)	5/14 (36)	50/74 (68)	0.02
Mortality at follow-up	4/14 (29)	7/75 (9)	0.07

* Deep cerebral venous system was defined as thrombosis in one or more of the following veins: internal cerebral veins, vein of Galen, and basal vein of Rosenthal. † Confirmed by MRI in 2/9 patients with hydrocephalus. IQR indicates interquartile range; mRS, modified Rankin Scale.

infratentorial localization of the hemorrhage. Intraventricular extension of the hemorrhage was present in one patient with hydrocephalus at baseline, compared to none among patients without hydrocephalus (7% versus 0%, p=0.15). This patient had a small amount of blood in the right occipital horn of the lateral ventricle.

Three different patterns of hydrocephalus could be discerned. The largest group consisted of patients with an increased rWTH, deep cerebral venous thrombosis and edema of the basal ganglia and thalami (Figure 2A, B). Nine of the 14 patients with hydrocephalus fitted this pattern. The BCI was normal in all of these patients, and only one had thrombosis of the superior sagittal sinus. The next group
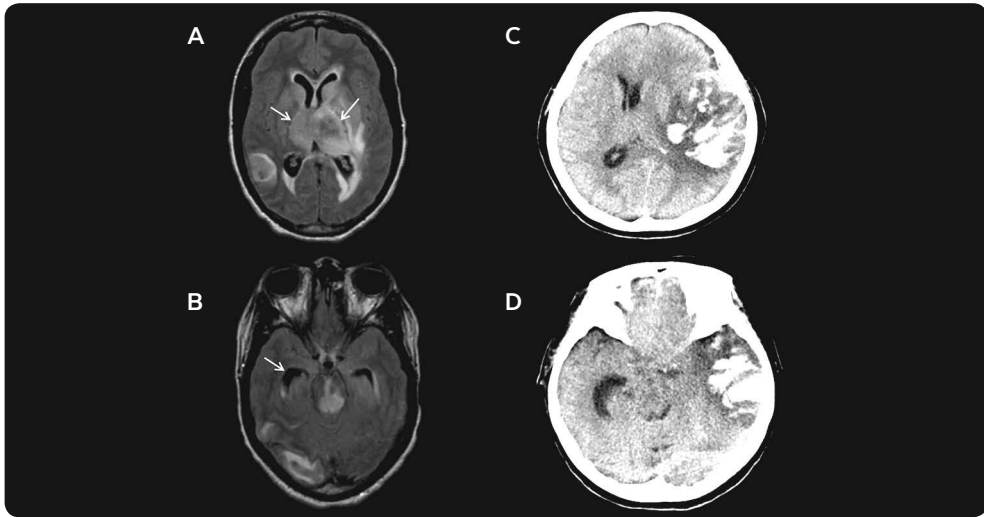
FIGURE 2. Cerebral imaging of 2 patients with hydrocephalus. *A and B: Axial Fluid Attenuated Inversion Recovery (FLAIR) MRI showing extensive edema in the thalami, basal ganglia and brainstem, and hydrocephalus of both temporal horns (arrows).* ***C and D****: Axial non contrast-enhanced CT-scan showing a large space occupying intracranial hemorrhage in the left hemisphere, and an increase of width of the contralateral temporal horn.*

consisted of three patients with an increased unilateral rWTH due to mass effect from a contralateral intracerebral hemorrhage (Figure 2C, D). Finally, two patients had an increased BCI without parenchymal lesions or thrombosis of the deep venous system. Both these patients had superior sagittal sinus thrombosis, without involvement of the deep veins.

Autopsy was performed in one patient with hydrocephalus and DCVT. Figure 3 shows a coronal section of the brain demonstrating widening of the temporal horns and small petechial hemorrhages and infarcts in the thalami. The third ventricle and foramen of Monro were narrowed.

All patients except one (in whom CVT was not diagnosed until autopsy) received treatment with therapeutic doses of heparin (Table 2). Patients with hydrocephalus more often were treated with endovascular thrombolysis (64% versus 18%, p<0.001) and more often underwent decompressive hemicraniectomy (21% versus 8%, p>0.1). One patient with hydrocephalus received an external ventricular drain, which was done prior to the diagnosis of CVT. This shunting procedure was done because of clinical worsening (decrease in consciousness) and for diagnostic reasons. At that time bacterial meningitis was considered the most likely diagnosis and previous
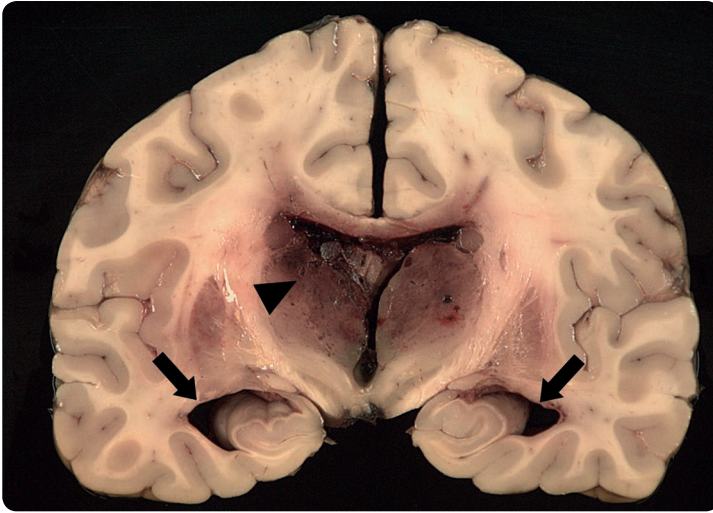
FIGURE 3. **Autopsy of a patient with hydrocephalus.** *Coronal section of the brain showing enlargement of the temporal horns (arrows). Small petechial hemorrhages and infarcts are present bilaterally in the thalami (arrowhead). The third ventricle and foramen of Monro are narrowed.*

attempts to obtain cerebrospinal fluid through lumbar puncture had failed. She suffered from acute lymphoblastic leukemia, which was diagnosed several hours after placement of the drain and died as a result of a massive intraventricular hemorrhage 1 day after admission. No shunting procedures were performed in any of the other patients with hydrocephalus. Two patients without hydrocephalus received a ventricular peritoneal drain because of intracranial hypertension with severe papilledema and impending blindness. Both patients recovered without visual loss.

Follow-up information on clinical outcome was available for 88 of the 93 patients (95%). While the duration of follow-up was non-significantly longer for patients with hydrocephalus (16 versus 8 months, p>0.1), patients with hydrocephalus less often had a good outcome at last available follow-up (36% versus 68%, p=0.02). Mortality was also higher in patients with hydrocephalus (29% versus 9%, p=0.07). After adjustment for baseline clinical imbalances (gender, focal neurological deficits, coma, and fixed pupils), however, hydrocephalus was not an independent predictor of outcome (adjusted OR for mRS 0-1, 0.67; 95% CI, 0.15-2.92).

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DISCUSSION

This is the first study on hydrocephalus in a large cohort of consecutive patients with cerebral venous thrombosis. Our data show that hydrocephalus predominantly occurs in patients with deep cerebral venous thrombosis and edema of the basal ganglia and thalami. In all patients with this pattern, the hydrocephalus is limited to the temporal horns of the lateral ventricle. It is unlikely that hydrocephalus in these patients is due to a diminished resorption of cerebrospinal fluid by the arachnoid villi. The majority of these villi are located in the superior sagittal sinus,[17] which was rarely occluded in these patients. A more plausible explanation and also consistent with the pattern of hydrocephalus, is that the flow of cerebrospinal fluid (CSF) through the foramen of Monro is obstructed due to local compression by edema of the basal ganglia and/or thalami. The autopsy results are in agreement with this hypothesis. Considering the pivotal role of the arachnoid villi in the drainage of CSF, one may wonder why CVT does not result in hydrocephalus more often, especially in cases with thrombosis of the superior sagittal sinus. Many of these patients have increased intracranial pressure, but hydrocephalus occurred only in 2/55 patients with thrombosis of the superior sagittal sinus in our cohort. The most likely explanation is that there is no pressure gradient of the CSF in these cases between the ventricular and subarachnoid compartments at the cerebral convexity. A similar mechanism has been proposed in patients with cryptococcal meningitis and increased intracranial pressure, who generally also do not have hydrocephalus.[18] Intraventricular extension of hemorrhage may also be a contributing factor to the development of hydrocephalus, but this occurred only in one patient.

The frequency of hydrocephalus was much higher in our cohort than previously reported.[5, 12] There are two possible explanations for this disparity. First, our hospital is a tertiary referral center for patients with a severe form of CVT. 21% of our patients was in coma at baseline and 17% had DCVT, which is both higher than in other cohort studies.[2, 19] A second explanation is that most studies did not focus on hydrocephalus, which probably lead to an underestimation of its frequency.

Despite aggressive treatment with endovascular thrombolysis and decompressive hemicraniectomy in many patients, hydrocephalus was associated with a high risk of poor outcome. After correction for baseline imbalances, however, hydrocephalus was not an independent predictor of outcome. Hydrocephalus is probably a marker of a severe form of CVT, associated with edema of the basal ganglia/thalami caused by DCVT. DCVT is a well-known predictor of poor outcome.[2] Since a causal relation between hydrocephalus and poor outcome is unlikely, the risks of shunting procedures and the fact patients with CVT require treatment with anticoagulation, we do not recommend routine shunting procedures in patients with CVT and hydrocephalus. Generally, we will only consider an external ventricular drain in these patients if they are in a worse clinical condition than would be expected on the extent of the parenchymal lesions or if they deteriorate without apparent cause other than

the hydrocephalus. In patients who additionally have seizures, the decision whether or not to perform a shunting procedure is even more difficult, since these patients often have fluctuations in their consciousness. The other situation when a shunting procedure should be considered in CVT is in patients with severe intracranial hypertension (usually without hydrocephalus) that comprises visual function or, rarely, cerebral perfusion.

Our study has some limitations – first, the rWTH is less often used for the determination of hydrocephalus than the BCI. Since cutoff values for a normal rWTH were not available in the literature, we determined the upper normal value by measuring the rWTH in a cohort of age-matched patients. Another limitation is that MRI – which is clearly superior to determine the extent of edema of the basal ganglia – was only available in a minority of patients. Finally, in a subset of patients, the data were collected retrospectively. However, since all imaging data were re-evaluated and outcome was available for almost all patients, we do not think this influences the validity of the results.

In conclusion, we found that hydrocephalus is more common in patients with cerebral venous thrombosis than previously believed. Hydrocephalus mainly occurs in patients with deep cerebral venous thrombosis and edema of the basal ganglia and thalami, probably because of obstruction of the foramen of Monro. The presence of hydrocephalus is associated with a worse clinical outcome, but a direct causal relation is unlikely. Routine shunting procedures are, therefore, not recommended in these patients.

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DECOMPRESSIVE HEMICRANIECTOMY IN SEVERE CEREBRAL VENOUS THROMBOSIS

a prospective case series

Susanna M. Zuurbier*, Jonathan M. Coutinho*, Charles B.L.M. Majoie
Bert A. Coert, Pepijn van den Munckhof, Jan Stam

Contributed equally

ABSTRACT

Background
Small retrospective case series suggest that decompressive hemicraniectomy can be life saving in patients with cerebral venous thrombosis (CVT) and impending brain herniation. Prospective studies of consecutive cases are lacking.

Methods
We performed a single centre, prospective study. In 2006 we adapted our protocol for CVT treatment to perform acute decompressive hemicraniectomy in patients with impending herniation, in whom the prognosis with conservative treatment was considered infaust. We included all consecutive patients with CVT between 2006 and 2010 who underwent hemicraniectomy. Outcome was assessed at 12 months with the modified Rankin Scale (mRS).

Results
Ten patients (8 women) with a median age of 41 years (range 26–52) were included. Before surgery 5 patients had GCS <9, 9 patients had normal pupils, 1 patient had a unilaterally fixed and dilated pupil. All patients except one had space–occupying intracranial hemorrhagic infarcts. The median preoperative midline shift was 9 mm (range 3–14 mm). Unilateral hemicraniectomy was performed in 9 patients and bilateral hemicraniectomy in one. Two patients died, from progressive cerebral edema and expansion of the hemorrhagic infarcts. Five patients recovered without disability at 12 months (mRS 0–1). Two patients had some residual handicap (one minor, mRS 2; one moderate, mRS 3). One patient was severely handicapped (mRS 5).

Conclusions
Our prospective data show that decompressive hemicraniectomy in the most severe cases of cerebral venous thrombosis was probably life saving in 8/10 patients, with a good clinical outcome in 6. In 2 patients death was caused by enlarging hemorrhagic infarcts.

INTRODUCTION

The standard treatment for cerebral venous thrombosis (CVT) is heparin and most patients recover well with this therapy. Approximately 20% of patients, however, remain handicapped or die.[1] The main cause of death is transtentorial herniation due large hemorrhagic infarcts.[2]

Retrospective case series suggest that decompressive hemicraniectomy can be life saving and result in good clinical outcome in such patients,[3, 4] sometimes even in seemingly hopeless cases.[5] A retrospective multinational registry of acute CVT cases undergoing decompressive surgery included 38 patients.[6] Twelve patients (32%) recovered completely [modified Rankin Scale (mRS) 0-1] and only 3 patients (8%) were severely dependent (mRS 4-5). Six patients (18%) died.[6] Retrospective studies, however, may overestimate the efficacy because of recall and selection bias. Confirmation in prospective studies is therefore required, but at present, these studies are not available. We prospectively examined all CVT patients who underwent decompressive hemicraniectomy in our hospital since 2006. Here we report the results of the first 5 years.

METHODS

Study population
We included all consecutive patients with CVT who presented to the Academic Medical Centre in Amsterdam, a tertiary care university hospital, between July 2006 and March 2011. Patients had decompressive craniectomy if they fulfilled the following criteria: (1) CVT confirmed by brain magnetic resonance imaging (MRI) with MRI-venography or computed tomographic-venography (CT-V). (2) Clinical signs of impending herniation, as defined by the presence of unilateral third nerve dysfunction and/or deterioration on the Glasgow Coma Scale (GCS). (3) The deterioration had to be the result of cerebral mass lesions (venous infarction or brain edema) and not attributable to seizures. The majority of the patients were transferred from other hospitals to our centre because of clinical deterioration. In 1 patient (case 10), CVT was diagnosed 1 day after evacuation of a 6x3x3 cm intracerebral hemorrhage from the left-sided temporal lobe. Because we considered decompressive craniectomy after July 2006 a standard treatment option for CVT patients with impending herniation, approval from the ethical committee was not required. As with any therapy, patients and family were counselled on the possible risks and benefits before treatment. The first cases have been published as a case report previously.[3]

Medical management
Patients were admitted to the department of neurology, neurosurgery or intensive care. Patients received heparin (unfractionated or low-molecular weight heparin) in

therapeutic doses immediately after they were diagnosed with CVT. During decompressive surgery, therapeutic heparin treatment was discontinued and continued only in prophylactic dose for at least 24 h post-operatively. Thereafter therapeutic dose heparin was restarted. In some patients prophylactic doses were given for a longer time because full dose heparin was considered too hazardous.

Decompressive hemicraniectomy

Decompressive hemicraniectomy consisted of the excision of a large bone flap and duraplasty. In summary, a large skin incision in the shape of a question mark based at the ear was made. A bone flap with a diameter of at least 12 cm including frontal, temporal and parietal bones was created. Since hemorrhagic infarcts in CVT are often large and frequently extend into the temporal lobe, we made special effort to extend the decompression toward the temporal skull base (Figure 1). The dura was opened widely to ensure maximal decompression. We did not resect any hemorrhagic infarcts, hematoma or brain parenchyma, except in case 10 where the diagnosis of CVT was made after evacuation of a hematoma. The cortical surface was covered with the unapproximated dural flaps and absorbable hemostatic cellulose (Surgicel®), after which only the skin was closed. In cases of severe intra-operative brain swelling, an ipsilateral intraparenchymatous intracranial pressure (ICP) transducer was implanted. Patients underwent post-operative brain CT within 24 hours. Re-implantation of the bone flap was performed within 12 months.

Outcome analysis and long-term follow-up

Follow-up visits at 6 and 12 months after the diagnosis. We assessed the outcome with the modified Rankin Scale (mRS; 0=complete recovery, 6=dead). We considered a mRS of 0, 1 or 2 (no disability or minor handicap) at 12 months the primary outcome. In case of missing values we imputed the last known score.
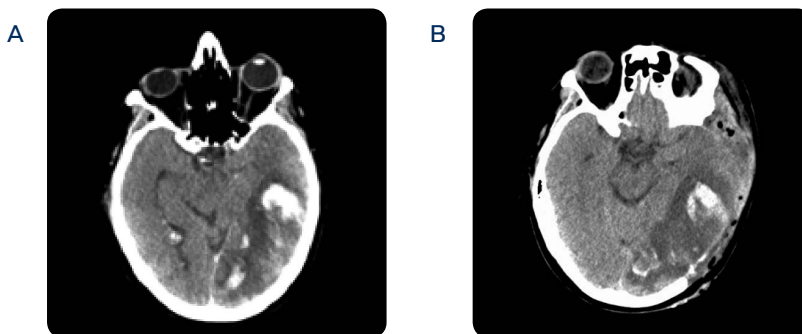
FIGURE 1. *A: Admission CT scan (of patient 4) shows left temporo-parieto-occipital hemorrhagic infarct.*
B: Direct post-operative CT scan, large decompression extending toward the temporal skull base.

Statistical analysis

Continuous variables are reported as medians. We used univariate logistic regression analysis to examine the association between clinical and radiological variables and outcome. The following variables were examined: age; gender; comatose before surgery; fixed and dilated pupil(s) before surgery; comatose after surgery, fixed and dilated pupil(s) after surgery; new or increased hemorrhagic lesion after surgery.

RESULTS

Baseline characteristics

Out of 56 CVT patients admitted in specified period, 10 patients (8 women and 2 men) were included. Compared to patients who did not receive decompressive surgery, those who underwent decompressive surgery had significantly more often intracranial hemorrhagic lesions, midline shift and were more frequently comatose (Table 1). Table 2 shows the individual baseline characteristics of the 10 included patients. The median age was 41 years (range 26–52 years). Median time from onset to diagnosis was 5 days (range 2–14 days) and from diagnosis to surgery was 2 days (range 0–4 days). Five patients were comatose before surgery and one had a unilateral fixed and dilated pupil. Six patients had one or more seizures before surgery.

TABLE 1. Comparison of baseline characteristics between CVT patients who did and did not undergo decompressive hemicraniectomy during 2006–2011.

	No DC	DC
Number of patients	46	10
Median age	42	41
Gender (% female)	67	80
Comatose (GCS <9) at admission (%)	7	30 *
Epileptic seizure(s) (%)	22	40
Hemorrhagic lesion(s) (%)	35	100 *
Midline shift (%)	13	100 *
Endovascular treatment (%)	9	10

*GCS indicates Glasgow Coma Scale; DC, decompressive craniectomy; * , p<0.05.*

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TABLE 2. Baseline characteristics.

Patient number	Sex (M/F)	Age (years)	Onset to diagnosis (days)	Diagnosis to surgery (days)	Before surgery GCS	Before surgery Pupils	Before surgery Seizures
1	M	39	4	2	E1M4Vt	+/+	−
2	F	36	3	2	E3M6V4	+/+	+
3	F	42	7	2	E1M5V1	+/+	+
4	F	52	8	0	E3M5V2	+/+	−
5	F	36	5	1	E3M5V2	+/+	+
6	M	52	2	0	E1M4Vt	+/+	+
7	F	37	6	0	E1M1Vt	+/+	+
8	F	29	2	0	E3M6V4	−/+	−
9	F	26	14	4	E2M5V2	+/+	+
10	F	52	4	4	E1M4Va	+/+	−

*GCS indicates Glasgow Coma Scale; **t**, tube; **a**, aphasia.*

Radiological examinations, surgery and post-operative condition

Results of the radiological examinations are shown in Table 3. The pre- and post-operative CT scans of all patients are shown in Figure 2. Six patients had left sided hemorrhagic infarcts, 2 patients had right-sided hemorrhagic infarcts and 2 patients had bilateral lesions. All patients had space-occupying intracranial hemorrhagic infarcts except 1 patient. This patient (case 9) had extensive subarachnoid bleeding and obliterated basal cisterns, and a bilateral craniectomy was performed. The median preoperative midline shift was 9 mm (range 3-14, Table 4). The median diameter of the bone flap was 15 cm (range 12-17 cm). Because of considerable brain swelling, an ICP transducer was implanted at the end of the procedure in three patients (cases 4, 6 and 9). The median post-operative midline shift was 4 mm (range 0-9). Three patients were comatose after surgery. Post-operatively, 8 patients had normal pupils; 2 had bilaterally fixed and dilated pupils. New hemorrhagic lesions occurred in 4 patients. In 1 patient (case 4), this new lesion occurred in the region of the ICP transducer, after its removal.

Additional interventions

Patient 7 underwent endovascular trombosuction 2 days after the hemicraniectomy because of lack of clinical improvement after decompressive hemicraniectomy, despite an uncomplicated procedure. She recovered with a minor handicap (mRS 2). Four patients needed additional operations. Two patients (cases 6 and 9) required re-operation because of progressive edema, expansion of the hemorrhagic infarcts and pathologically elevated ICP. Both underwent enlargement of the decompressive craniectomy, but both died. Patient 10 developed a cerebral abscess

Pre operative   Post operative   Pre operative   Post operative

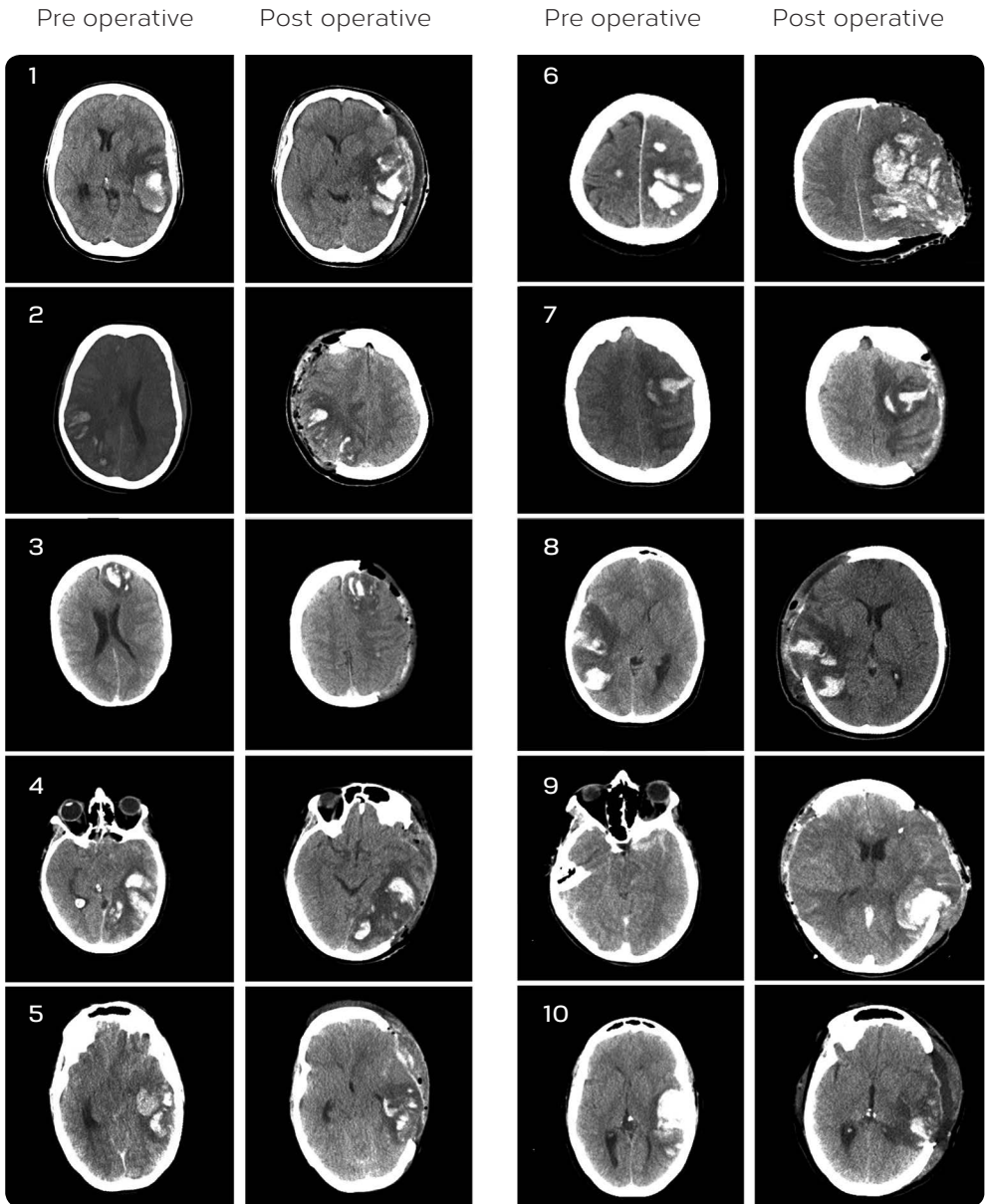**FIGURE 2.** Pre- and post-operative CT scans of all 10 cases. *All patients had space-occupying intra-cranial hemorrhagic infarcts except case 9. Case 9 had extensive subarachnoid bleeding, small bilateral hemorrhages, generalized cerebral edema and obliterated basal cisterns. Case 3 had besides the hemor-rhagic infarct obliterated basal cisterns due to increased bilateral cerebral edema.*

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TABLE 3. Radiological findings.

Patient number	Thrombosed sinuses	Hemorrhagic infarcts	Volume lesion (cm3)	Midline shift pre operative (mm)	Bilateral lesions	Location hemorrhagic infarcts
1	STL, SSL, CV	+	110	12	–	Left temporal
2	SSS, CV	+	133	9	–	Right parieto–occipital
3	SSS, SR, CV	+	39	4	–	Left frontal
4	STL, SSL, SR, DCS, CL, CV	+	78	14	–	Left temporo–parieto–occipital cerebellar
5	STL, SSL, SR, DCS, CL, CV	+	165	12	–	Left temporo–occipital, cerebellar
6	SSS, SR, JL, CV	+	102	7	+	Left fronto–parietal, right parietal
7	SSS, STR, SSR, CV	+	58	5	–	Left frontal
8	STR, SSR, CV	+	161	9	–	Right temporo–occipital
9	SSS, STL, STR, SSL, SSR, SR, JL, JR, CV	+	1 *	3	+	Left parietal, right parietal extensive subarachnoid bleeding
10	STL, SSL, JL, CV	+	152	10	–	Left temporo–parieto–occipital

*Extensive subarachnoid bleeding and obliterated basal cisterns. **SSS** indicates superior sagittal sinus; **ST**, transverse sinus (R, right; L, left); **SR**, sinus rectus (=straight sinus); **SS**, sinus sigmoidius (R, right; L, left); **CV**, cortical vene; **DCS**, deep cerebral venous system; **C**, cerebellar vein (R, right; L, left); **J**, jugular vein (R, right; L, left);*

and subdural empyema at the site of the hemicraniectomy which was surgically removed. She also developed bacterial meningitis and hydrocephalus, and needed an external ventricular drain, which was later converted to a ventricular peritoneal shunt. Patient 4 developed an epidural hematoma after re-implantation of the bone flap and subsequently had two re-operations.

Clinical outcome

Two patients died during the primary hospital admission (Table 5). Six patients had a good clinical outcome (mRS0-2) at 12 months. Two patients had a moderate or severe residual handicap: patient 4 had a severe expressive aphasia and a right-sided homonymous hemianopia (mRS 3). Patient 10 is still bedridden and incontinent after 6 months (mRS 5). All surviving patients received oral anticoagulation for a period of 6-12 months. Six patients had seizures during follow-up, 5 of them still at 12 months. Despite the small sample size we attempted to identify prognostic variables using univariate logistic regression analysis. There was a trend that

TABLE 4. Surgical characteristics and outcome.

Patient number	Inter- vention	Midline shift (mm)	GCS	Pupils	New hemor- rhage	Additional interventions	mRS 6 months	mRS 12 months
1	U	7	E4M6Va	+/+	–	–	2	1
2	U	4	E4M6V5	+/+	–	–	1	1
3	U	0	E1M5Vt	+/+	–	–	1	1
4	U	3	E3M5Vt	+/+	+	–	3	3
5	U	2	E3M6V2	+/+	–	–	1	1
6	U	9	E1M1Vt	–/–	+	Enlarging hemicraniectomy	6	6
7	U	4	E3M5Vt	+/+	+	Thrombosuction	2	2
8	U	0	E4M6V5	+/+	–	–	2	0
9	B	4	E1M1Vt	–/–	+	Enlarging hemicraniectomy	6	6
10	U	0	E4M6Va	+/+	–	Evacuation subdural empyema	5	*

* 12 months outcome not yet available. U indicates unilateral hemicraniectomy; B, bilateral hemicraniec-tomy; GCS, Glasgow Coma Scale. t; tube; a, aphasia; mRS, modified Rankin Scale.

new hemorrhagic lesions after surgery was associated with a poor outcome at 12 months (odds ratio, 0.07; 95% CI, 0.003–1.51, p=0.09). No other prognostic factors were identified.

DISCUSSION

This is the first prospective cohort study of ten CVT patients with impending trans-tentorial herniation undergoing decompressive craniectomy. Six patients had good functional recovery after 1 year. Two patients died despite intervention. The largest study so far on this subject is a combination of a retrospective multinational registry and systematic review of published cases,[6] with outcome data of 69 patients. Forty-five patients had decompressive craniectomy, 7 hematoma evacuation, and 17 patients underwent both types of surgery. Compared to our study, both mortality (16% versus 20%) and the percentage of patients who were functionally inde-pendent at follow-up (57% versus 60%) were similar (Table 5). However, patients from this retrospective study were generally in a worse clinical condition prior to surgery; 72% were comatose, compared to 50% in our study, and 57% had single or bilateral fixed and dilated pupils, compared to 10% in our cohort.

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Transtentorial herniation is the most common cause of death during the acute stage of CVT.[2] Prior to 2006, before we adopted our policy to perform decompressive craniectomy, most of our CVT patients with impending transtentorial herniation died despite maximal conservative treatment and endovascular thrombolysis.[7] A recent French study also showed a large difference in mortality between patients who did or did not undergo decompressive craniectomy, in favour of surgical intervention.[4] The most plausible explanation is that craniectomy removes the immediate threat of fatal herniation, analagous to the effect of craniectomy in ischemic stroke.[8]

We tried to make the craniectomy wide and to extent decompression toward the temporal skull base. If the craniectomy is too small, the decompressive effect may not be sufficient to prevent or reverse transtentorial herniation. Re-operation to enlarge the decompression was performed in 2 patients who did not clinically improve after craniectomy and in whom post-operative ICP remained pathologi-cally elevated. Nevertheless, both patients died from intractable expanding cerebral hemorrhagic infarcts.

TABLE 5. Comparison of oucomes with retrospective data.

	Ferro et al[6]	Current study
Design	Retrospective	Prospective
Number of patients	69	10
Median age	42	41
Comatose before surgery (%)	72	50
Fixed and dilated pupil(s) before surgery (%)	57	10
Hemorrhagic lesions (%)	90	100
Independence at follow-up (mRS 0-2) (%)	57	60
Mortality (%)	16	20

mRS indicates modified Rankin Scale.

The large number of patients who underwent decompressive craniectomy in our study (10 out of 56; 18%) cannot be extrapolated to CVT patients in general. Our hospital serves as a tertiary care centre for CVT patients in the Netherlands. While milder cases are usually treated at local hospitals, neurologists tend to refer severe cases to our centre. Therefore, the percentage of all CVT patients undergoing decompressive surgery is certainly much lower than the 18% in our study.

A reason why clinicians may be reluctant to perform decompressive craniectomy could be the fear that it may reduce mortality at the expense of an increase of severely

disabled survivors. A randomized trial on decompressive craniectomy for ischemic stroke indeed showed a fivefold increase in severely disabled patients (mRS 4 or 5).[8] This concern does not seem warranted in CVT patients. While the decision to perform decompressive craniectomy must still be carefully weighed in each case, the large percentage of patients with a good functional outcome justifies a positive stance regarding this intervention. Moreover, withholding craniectomy in these patients will result in death by herniation in nearly all cases. The relatively low number of severely disabled survivors is probably due to the fact that venous infarcts in general have more potential for recovery than arterial infarcts.[9] For the same reason, we prefer not to evacuate the venous infarct or hematoma during the decompressive surgery, except when this is considered the last resort to reverse the herniation process.

New hemorrhagic lesions were identified on post-operative imaging in 4 out of 10 patients and tended to be associated with poor outcome. Both patients who died had expanding hemorrhagic infarcts with new hemorrhagic areas after surgery. The etiology of new lesions is unclear. One possibility is that the elevated pre-operative ICP prevents the development, or enlargement, of hemorrhagic lesions, and that new hemorrhagic lesions develop when the ICP decreases following craniectomy. We did not systematically measure ICP during surgery, so we cannot examine whether there was an association between ICP and new hemorrhagic lesions. Another possibility is that developing collateral venous systems draining to the skull or scalp may be damaged during surgery.[10] Thirdly, we cannot exclude that new hemorrhagic lesions resulted from direct manipulation of the cortex during surgery or during post-operative removal of ICP transducers. Finally, the need to interrupt or reduce the heparin might cause extension of the thrombus and occlusion of (new) cortical veins.

The currently available evidence suggests that decompressive craniectomy often results in good functional outcome in CVT patients with impending transtentorial herniation. Obviously, additional prospective data on its efficacy are needed. However, we believe that a randomized controlled trial faces insurmountable ethical objections since most of these patients will die if left untreated.[2, 4, 7] Instead, an international prospective registry of consecutive cases would be preferable. Currently, efforts are being undertaken to initiate such a project. Until that time, however, we believe that decompressive craniectomy should be strongly considered in CVT patients who have both clinical and radiological sign of impending herniation.

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ACKNOWLEDGEMENT

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SUMMARY AND GENERAL DISCUSSION

INTRODUCTION

Cerebral venous thrombosis (CVT) is an important cause of stroke, especially in the young. Due to the variability of clinical manifestations, CVT can be difficult to diagnose. Patients with CVT have a thrombotic occlusion of one or more of the dural sinuses of the brain, usually in combination with cortical vein thrombosis. CVT leads to a diminished outflow of blood and cerebrospinal fluid, which in about 50% of patients results in the development of a venous (hemorrhagic) infarct, and to intracranial hypertension in about 20%. The standard treatment of CVT consists of therapeutic doses of heparin. In severe cases, endovascular treatment can be considered, but more evidence on its efficacy and safety is required. Increased awareness of the diagnosis of CVT, improved cerebral imaging techniques and more effective treatments have improved the prognosis of CVT. Nevertheless, CVT is still a serious condition, with a mortality rate of 5-10%. This thesis describes the results of studies we performed on the epidemiology, clinical course, and outcome of CVT.

PART I   EPIDEMIOLOGY

Chapter 2 is a cross-sectional study of the incidence of CVT among adults in the Netherlands. Before our study, estimates of the incidence ranged from 0.2 to 0.5 per 100.000, based on an extrapolation of old mortality data and therefore in accurate. We performed a retrospective study among all 19 hospitals located in 2 Dutch provinces. By hand searching the medical records of potential patients, we identified adult CVT cases admitted during a time span of 3 years. Among 9270 potential cases, we identified 94 cases of CVT, which gives an estimated incidence of 1.32 per 100.000 person-years (95% confidence interval (CI) 1.06 to 1.61). Our data shows that the incidence of CVT among adults is higher than previously believed.

Chapter 3 is a systematic review of the literature on the change in sex ratio over time in patients with CVT. Studies with 40 patients with CVT or more that reported sex ratio were eligible. We ranked studies according to the year halfway the period of patient recruitment. Out of 6068 potentially eligible studies, 112 fulfilled the selection criteria. Data from 23.638 patients with CVT, included between 1966 and 2014, were analyzed. The proportion of women among patients with CVT significantly increased over time from a median of 54.8% in studies prior to 1981 to 69.8% after 2001 (p=0.002). There was a significant correlation between time of the study and proportion of women (Pearson correlation coefficient 0.25, p=0.01). Oral contraceptive use among women with CVT also increased over time (Pearson correlation coefficient 0.29, p=0.01). In contrast, the percentage of pregnancy-related cases remained stable (Pearson correlation coefficient 0.04, p=0.77). Among 1702 patients from pediatric studies, 39% were female and there was no correlation between sex ratio and time of the study (Pearson correlation coefficient -0.42, p=0.14). Our data confirm that there

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is a shift in sex ratio in adults over time with an increase in the proportion of women, whereas the sex ratio among children remains constant. A possible explanation for this phenomenon is an increase over time in the use of oral contraceptives.

Chapter 4 is a case-control study in which we examined if obesity is a risk factor for CVT. Cases were adult patients with CVT. For controls, we assessed subjects from the control population of the MEGA study (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis), a large Dutch case-control study in which risk factors for deep venous thrombosis and pulmonary embolism were assessed. A multiple imputation procedure was used for missing data. Subjects with a normal weight (body mass index (BMI) <25 kg/m^2) were the reference category. We included 186 cases and 6134 controls. Obesity (BMI ≥30 kg/m^2) was associated with an increased risk of CVT (adjusted odds ratio (OR) 2.63, 95% CI 1.53-4.54). Stratification by sex showed that there was a strong association between CVT and obesity in women (adjusted OR 3.50, 95% CI 2.00-6.14), but no association in men (adjusted OR 1.16, 95% CI 0.25-5.30). Further stratification showed that in women who used oral contraceptives, overweight and obesity were associated with an increased risk of CVT in a dose-dependent manner, compared to women of normal weight who did not use oral contraceptives (BMI 25-29.9: adjusted OR 11.87, 95% CI 5.94-23.74; BMI ≥30: adjusted OR 29.26, 95% CI 13.47-63.60). There was no association in women who did not use oral contraceptives. Our study shows that obesity is a strong risk factor for CVT in women who use oral contraceptives.

In **chapter 5** we examined in a systematic review of the literature if CVT associated mortality declined over time. Out of 4585 potentially eligible studies, 74 fulfilled the selection criteria. Data from 8829 patients with CVT, included between 1942 and 2012, were analyzed. The average age was 32.9 years, and 64.7% were women. We found an inverse correlation between mortality and year of patient recruitment (Pearson correlation coefficient -0.72, p<0.001). The correlation remained statistically significant in a sensitivity analysis, after exclusion of studies published before 1990, retrospective studies, or single-center studies. The frequency of coma and focal neurological deficits also decreased significantly over time (correlation coefficient -0.52, and -0.50, respectively). Our data confirm that there is a clear trend in declining mortality among patients with CVT over time. Possible explanations are improvements in treatment, a change in risk factors, and identification of less severe cases by improved diagnostic methods.

PART II   CLINICAL COURSE AND OUTCOME

In **chapter 6** we report a retrospective study to describe the clinical course of CVT in a cohort of 240 adults with leukemia. All 240 patients were treated for newly diagnosed acute lymphoblastic leukemia (ALL) in the HOVON (Dutch-Belgian Hemato-Oncology

Cooperative Group) 37 study. We conducted a nested case–control design to explore the relevance of early symptoms and risk factors for CVT in ALL patients. Nine of the 240 ALL patients developed CVT (3.8%, 37.5% of all venous thrombosis). CVT occurred during or shortly after the initiation of asparaginase therapy in 8 cases and shortly after intrathecal methotrexate injections in all cases, during cycle I of induction treatment. CVT was strongly associated with headache (OR, 28; 95% CI, 3–296) and seizures (OR∞). Five patients with CVT died during the first 12 months of their HO37 treatment, while the overall mortality at 12 months was 29.2%. Patients with CVT less often obtained complete remission than patients without CVT after cycle I of remission induction treatment (44.4% versus 82.7%; OR, 0.17; 95% CI, 0.04–0.65) and after the complete treatment protocol (55.6% versus 90.5%; OR, 0.13; 95% CI, 0.03–0.53). We concluded that CVT is a relatively common venous thrombotic complication in adult patients with ALL. It is likely caused by the additive effects of multiple risk factors, with a particular role for asparaginase and the effects of lumbar punctures for intrathecal therapy. CVT in adult patients with ALL is associated with a high mortality rate and a worse result of ALL treatment.

Chapter 7 describes a cohort study about admission hyperglycemia in adult patients with CVT. Patients were included at the Academic Medical Centre in The Netherlands and in the Helsinki University Central Hospital, Finland. We excluded patients with known diabetes mellitus and patients without known admission blood glucose. We defined admission hyperglycemia as blood glucose ≥7.8 mmol/L (141 mg/dL) and severe hyperglycemia as blood glucose ≥11.1 mmol/L (200 mg/dL). Of 380 patients with CVT, 308 were eligible. Of these, 66 (21.4%) had admission hyperglycemia, which was severe in 8 (2.6%) cases. Patients with admission hyperglycemia had a higher risk of a poor outcome (modified Rankin Scale -mRS- score of 3 to 6; adjusted OR, 3.10; 95% CI, 1.35–7.12) and mortality (adjusted OR, 4.13; 95% CI, 1.41–12.09). Severe hyper-glycemia was associated with higher risks of poor outcome (mRS 3 to 6; adjusted OR, 11.59; 95% CI, 1.74–77.30) and death (adjusted OR, 33.36; 95% CI, 3.87–287.28) compared to normoglycemic patients. Our study shows that admission hypergly-cemia is a strong predictor of poor clinical outcome in patients with CVT.

In chapter 8, we used data of the International Study on Cerebral Venous and dural sinus Thrombosis (ISCVT), a multi-center prospective observational study to explore the difference between adult CVT patients with and without an infection of the head or neck. 604 of 624 patients were eligible for the study. 57 patients had an infection of the head or neck (9.4%). New intracerebral hemorrhages were more common in patients with an infection (12.3% versus 5.3%, p=0.04) but the rate of poor outcomes (death or dependency) did not differ between patients with and without an infection (15.8% versus 13.7%). About 4/5 of all patients were treated with therapeutic doses of heparin, irrespective of the presence or absence of an infection of the head or neck (82.5% and 83.7%, respectively). Among the patients with an infection of the head or neck, there was no significant difference in the

frequency of new intracerebral hemorrhages and poor outcome between those who did or did not receive therapeutic doses of heparin. We concluded that new intracerebral hemorrhages were more frequent in patients with an infection, but the use of therapeutic doses of heparin did not appear to influence the risk of new intracranial hemorrhages or poor clinical outcome. However, the number of patients who did not receive heparin was too small to draw conclusions about safety of heparin in adults with CVT and an infection of the head or neck.

In **chapter 9** we examined the frequency, pathophysiology and clinical manifestations of hydrocephalus in patients with CVT, admitted to the Academic Medical Center in Amsterdam between 2000 and 2010. We excluded patients in whom hydrocephalus was caused by a disease other than CVT or if it was iatrogenic. 14 of 92 patients with CVT had hydrocephalus (15.2%). Patients with hydrocephalus more often had focal neurological deficits (85.7% versus 49.4%, p=0.02) and were more frequently comatose (42.9% versus 16.4%, p=0.06), as compared to patients without hydrocephalus. Thrombosis of the deep cerebral venous system (64.3% versus 8.9%, p<0.001) and edema of the basal ganglia and thalami (64.3% versus 3.8%, p<0.001) were more common in patients with hydrocephalus. Outcome at follow-up was worse in patients with hydrocephalus (mRS $\geq$2, 64.3% versus 32.4%, p=0.02; mortality 28.6% versus 9.3%, p=0.07). We concluded that hydrocephalus occurs more frequently in CVT than previously observerd, especially in patients with deep cerebral venous thrombosis and edema of the basal ganglia, probably related to an obstruction of the foramen of Monro.

Chapter 10 describes the efficacy of decompressive hemicraniectomy in ten patients with severe CVT and impending cerebral herniation, at the time of publication the largest prospective study of this intervention for CVT. The median age of the patients was 41 years (range 26–52). Five patients were comatose before surgery. All patients except one had space-occupying intracranial hemorrhagic infarcts. The median preoperative midline shift was 9 mm (range 3–14). Two patients died from progressive cerebral edema and expansion of the hemorrhagic infarcts. Of the 8 surviving patients, 6 had a good outcome (no disability in 5; minor disability in one). Decompressive hemicraniectomy can be life saving and can result in an excellent outcome in patients with severe CVT and impending cerebral herniation.

FUTURE PERSPECTIVES

Oral anticoagulants

There are no controlled trials assessing the optimal duration of oral anticoagulation in patients with CVT. Current management is based on expert consensus and individual patient risks and preferences. Therefore, an international prospective study (EXCOA; the benefit of extending oral anticoagulation treatment after acute cerebral

vein thrombosis, principal investigator: prof. dr. J.M. Ferro) with a cluster allocation design was launched in 2014. The purpose of the EXCOA study is to compare the efficacy and safety of a short (3-6 months) versus long-term (12 months) approach with oral anticoagulation for the prevention of venous thrombosis after an episode of CVT. Patients will be followed up for a total of 24 months to assess the risk of recurrent venous thrombotic events after stopping oral anticoagulation.

Endovascular treatment

Endovascular treatment may be beneficial for a subgroup of patients with CVT, who have a poor prognosis despite treatment with heparin. Published experience with endovascular treatment is promising, but only based on uncontrolled studies. The objective of the TO-ACT (Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis) trial is to examine if endovascular treatment improves the functional outcome of patients with CVT. The TO-ACT trial is a multi-centre, prospective, randomized, open-label, blinded endpoint trial (principal investigators: prof. dr. J. Stam, prof. dr. J.M. Ferro, prof. dr. M.G. Bousser; trial coordinator: J.M. Coutinho). Patients are eligible if they have a radiologically proven CVT, a high probability of poor outcome (defined by presence of one or more of the following risk factors: mental status disorder, coma, intracranial hemorrhagic lesion, or thrombosis of the deep cerebral venous system) and if the responsible physician is uncertain whether endovascular treatment or standard anticoagulant treatment is better. 164 patients will be included. Patients are randomized to receive either endovascular treatment or standard treatment (therapeutic doses of heparin). Endovascular treatment consists of local application of rt-PA or urokinase within the thrombosed sinuses, mechanical thrombectomy, or a combination of both. The primary endpoint is the mRS at 12 months. Secondary outcomes are 6 months mRS, mortality and recanalization rate. Principal safety outcomes are major intra- and extracranial hemorrhagic complications. The first patient was randomized in September 2011. Currently, 64 patients have been recruited by 14 hospitals from five countries (www.to-act-trial.org).

Decompressive hemicraniectomy

To obtain more data on the efficacy of decompressive hemicraniectomy in patients with severe CVT, we participate in the DECOMPRESS-2 study (principal investigator prof. dr. J.M Ferro), an international prospective registry. Participating centers record data on a case record form of clinical and radiological information of consecutive adults with CVT treated by decompressive hemicraniectomy or hematoma evacuation. Clinical recovery and quality of life is measured at 6 and 12 months follow-up. The first patient was included in January 2012.

Other ongoing research

We have an ongoing prospective CVT registry in the Academic Medical Center since 2006. Data on baseline characteristics, radiological findings, and treatment of CVT patients are systematically recorded. Several ongoing research projects are

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in part based on this database. We participate in a multicenter study with the aim to determine the sensitivity and specificity of non-contrast CT to diagnose CVT (principal investigator prof. dr. V. Thijs). We also recently started a pilot study to evaluate the feasibility of using the pulsatility index by transcranial color-coded duplex sonography to determine intracranial pressure in patients with CVT. In 2012, together with colleagues from Inselspital (principal investigator prof. dr. M. Arnold) we started a study to assess the overall accuracy of D-dimer values and FXIII activation peptide, to exclude CVT in patients with clinical suspicion of CVT. Together, we have collected blood samples and clinical information from more than 350 patients with suspected CVT, and the data will be analyzed in 2016. To better understand the genetic basis of CVT, we participate in the BEAST (Biorepository to Establish the Aetiology of Sinovenous Thrombosis) study, which aims to identify candidate genes associated with CVT by genome sequencing of a large number of CVT cases (principal investigator prof. dr. P. Sharma).

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APPENDICES

LIST OF ABBREVIATIONS

ALL	acute lymphoblastic leukaemia
BCI	bicaudate index
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CR	complete remission
CSF	cerebrospinal fluid
CT	computed tomography
CVT	cerebral venous thrombosis
DC	decompressive craniectomy
DCVT	internal cerebral veins, vein of Galen, and/or the basal vein of Rosenthal
DVT	deep vein thrombosis
ENT	ear-nose-throat
ET	endovascular thrombolysis
FLAIR	fluid attenuated inversion recovery
GCS	glasgow coma scale
HO37	Dutch-Belgian HOVON-37 ALL
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
IQR	interquartile range
ISCVT	international study on cerebral vein and dural sinus thrombosis
LMWH	low molecular weight heparin
M	multi-center
MEGA	multiple environmental and genetic assessment of risk factors for venous thrombosis
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MRV	magnetic resonance venography

MTX	methotrexate
NA	not applicable
NR	not reported
OC	oral contraceptive
OR	odds ratio
P	prospective
R	retrospective
rWTH	radial width of the temporal horn
S	single-center
SD	standard deviation
TO-ACT	Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis
UFH	unfractionated heparin
VTE	venous thromboembolism

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NEDERLANDSE SAMENVATTING

INLEIDING

Cerebrale veneuze trombose (CVT), ook wel sinustrombose genoemd, is een belangrijke cerebrovasculaire aandoening die vooral bij jongere patiënten voorkomt. Door de variabiliteit in de klinische presentatie is het soms moeilijk om de diagnose te stellen. CVT is het gevolg van een bloedstolsel in de aders. Hierdoor kan het bloed niet goed uit de hersenen worden afgevoerd en dat leidt bij ongeveer 50% van de patiënten met CVT tot de ontwikkeling van een veneus (hemorragisch) herseninfarct. De standaardbehandeling bestaat uit de toediening van heparine in therapeutische dosering. In ernstige gevallen kan endovasculaire behandeling worden overwogen, maar de effectiviteit van deze behandeling is nog niet aangetoond. Bij dreigende inklemming kan een decompressieve hemicraniëctomie levensreddend zijn. De prognose is verbeterd door een betere herkenning van de ziekte, verbeterde beeldvormingstechnieken en effectievere behandelingen. Toch is CVT nog steeds een ernstige aandoening, met een sterfte van 5% tot 10%. Dit proefschrift beschrijft de resultaten van onderzoeken die wij hebben uitgevoerd, gericht op de epidemiologie, het klinische beloop en de uitkomst van CVT.

DEEL 1: EPIDEMIOLOGIE

In **hoofdstuk 2** presenteren wij nieuwe gegevens over de incidentie van CVT bij volwassenen. De incidentie werd eerder geschat op 0.2 tot 0.5 nieuwe gevallen per 100.000, gebaseerd op een extrapolatie van oude sterftecijfers. Wij hebben een retrospectief dwarsdoorsnede onderzoek verricht onder alle 19 ziekenhuizen in twee Nederlandse provincies. Aan de hand van medische dossiers hebben wij volwassen patiënten met een CVT geïdentificeerd gedurende een periode van 3 jaar. Er werden 9270 potentiële patiënten gescreend. Daarvan waren 94 nieuwe gevallen van CVT. Met deze gegevens hebben wij een incidentie berekend van 1.32 nieuwe gevallen per 100.000 persoonsjaren. Ons onderzoek toont aan dat de incidentie van CVT onder volwassenen hoger is dan eerder werd gedacht.

Hoofdstuk 3 gaat over de verschuiving van de sekse ratio in de afgelopen decennia. Hiervoor analyseerden we alle artikelen over minimaal 40 patiënten met CVT met voldoende gegevens om de sekse ratio te bepalen. In totaal voldeden 112 artikelen

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aan deze criteria, met daarin gegevens van 23.638 patiënten. Het percentage vrouwen met CVT nam toe in de tijd: in studies van vóór 1981 was dat mediaan 54.8%, en dat percentage liep op tot mediaan 69.8% in publicaties van na 2001 (p=0.002). Er is een significante positieve correlatie tussen het percentage vrouwen en het jaar van inclusie (Pearson correlatie coëfficiënt 0.25, p=0.01). Het gebruik van orale anticonceptiva onder vrouwen met CVT is toegenomen in de loop van de tijd (Pearson correlatie coëfficiënt 0.29, p=0.01) terwijl het percentage zwangerschap-gerelateerde gevallen stabiel bleef (Pearson correlatie coëfficiënt 0.04, p=0.77). Onder de 1702 kinderen met CVT was 39% van het vrouwelijk geslacht, en er was geen correlatie tussen sekse ratio en het jaar van inclusie (Pearson correlatie coëfficiënt −0.42, p=0.14). Dit onderzoek bevestigt dat het percentage volwassen vrouwen onder de patiënten met CVT sterk is gestegen in de laatste 50 jaar, terwijl de sekse ratio bij kinderen niet is veranderd. Vermoedelijk is de belangrijkste oorzaak van deze verschuiving de toename van het gebruik van orale anticonceptiva.

Hoofdstuk 4 is een patiënt-controle onderzoek waarin we hebben onderzocht of obesitas een risicofactor is voor CVT. Patiënten waren volwassenen met CVT, en controles waren volwassenen uit de controlegroep van de MEGA studie, een groot patiënt-controle onderzoek naar risicofactoren voor diep veneuze trombose en longembolie. Personen met een normaal gewicht (body mass index (BMI) <25 kg/m^2) vormden de referentie-categorie. We includeerden 186 patiënten en 6134 controles. Obesitas (BMI >30 kg/m^2) was geassocieerd met een verhoogd risico op CVT (gecorrigeerde odds ratio [OR], 2.63; 95% betrouwbaarheidsinterval [CI], 1.53–4.54). Stratificatie naar geslacht toonde aan dat er een sterke associatie was tussen CVT en obesitas bij vrouwen (gecorrigeerde OR, 3.50; 95% CI, 2.00–6.14), maar niet bij mannen (gecorrigeerde OR, 1.16; 95% CI, 0.25–5.30). Verdere stratificatie toonde aan dat bij vrouwen die orale anticonceptiva gebruikten obesitas geassocieerd was met een verhoogd risico op CVT, in vergelijking met vrouwen met een normaal gewicht die geen orale anticonceptiva gebruikten (BMI 25–29.9: gecorrigeerde OR, 11.87; 95% CI, 5.94–23.74; BMI >30: gecorrigeerde OR, 29.26; 95% CI, 13.47–63.60). Bij vrouwen die geen orale anticonceptiva gebruikten was er geen relatie tussen obesitas en CVT (gecorrigeerde OR, 1.29; 95% CI, 0.46–3.660). Dit onderzoek toont aan dat obesitas een sterke risicofactor is voor CVT bij vrouwen die orale anticonceptiva gebruiken.

Hoofdstuk 5 is een systematische analyse van de literatuur over de sterfte bij CVT in de afgelopen decennia. In totaal werden 74 artikelen geïncludeerd, met daarin de gegevens van 8829 patiënten. Er was een significante negatieve correlatie tussen sterfte en het jaar van inclusie (Pearson correlatie coëfficiënt −0.72). Dit onderzoek bevestigt dat er een duidelijke daling is van de sterfte bij CVT gedurende de afgelopen decennia. Mogelijke verklaringen hiervoor zijn een verandering in risicofactoren, de identificatie van minder ernstige gevallen door verbeterde diagnostische methoden en verbeteringen van de behandeling.

DEEL 2: KLINISCH BELOOP EN UITKOMST

Hoofdstuk 6 beschrijft een retrospectief onderzoek naar het klinische beloop van CVT in een cohort van 240 volwassenen behandeld voor acute lymfatische leukemie (HOVON-37 studie). Negen van de 240 patiënten (3.8%, 37.5% van alle veneuze trombo-embolieën) werden gediagnosticeerd met CVT. CVT trad op kort na de toediening van L-asparaginase (bij 8 patiënten) en werd bij alle patiënten voorafgegaan door intrathecale methotrexaat injecties. Patiënten met CVT hadden vaak hoofdpijn en epileptische aanvallen. De totale sterfte in de eerste 12 maanden onder de 240 volwassenen behandeld voor acute lymfatische leukemie was 29.2%. Vijf patiënten met CVT overleden in de eerste 12 maanden (55.6%). CVT is een frequente complicatie van acute lymfatische leukemie, waarschijnlijk veroorzaakt door het effect van verschillende risicofactoren, in het bijzonder L-asparaginase behandeling en de intrathecale toediening van methotrexaat.

Hoofdstuk 7 is een cohort onderzoek naar de relatie tussen hyperglycemie bij presentatie in het ziekenhuis en de klinische uitkomst van patiënten met CVT. Hyperglycemie werd gedefinieerd als een bloedglucose concentratie ≥7.8 mmol/L (141 mg/dL). Van de 380 patiënten met CVT werden 308 patiënten geïncludeerd in dit onderzoek, waarvan 66 (21.4%) patiënten hyperglycemie hadden. Patiënten met hyperglycemie hadden vaker een slechte klinische uitkomst (modified Rankin Scale score van 3 tot en met 6, gecorrigeerde OR, 3.10; 95% CI, 1.35-7.12), en over-leden vaker (gecorrigeerde OR, 4.13; 95% CI, 1.41-12.09). Dit onderzoek toont aan dat hyperglycemie bij presentatie bij patiënten met CVT geassocieerd is met een slechte klinische uitkomst.

Hoofdstuk 8 gaat over de presentatie, behandeling en klinische uitkomst van pati-enten met CVT gerelateerd aan een infectie van het hoofd of de hals. Hiervoor hebben we de data van de "International Study on Cerebral Vein and dural sinus Thrombosis" (ISCVT) gebruikt. De ISCVT is een groot prospectief, multicenter, cohort onderzoek. In totaal werden 604 van de 624 patiënten geïncludeerd in ons onderzoek. 57 van hen hadden een infectie van het hoofd of de hals (9.4%). Nieuwe intracerebrale bloedingen kwamen vaker voor bij patiënten met een infectie van het hoofd of de hals (12.3% versus 5.3%, p=0.04). Sterfte en een slechte klinische uitkomst (modified Rankin Scale score van 3 tot en met 6) verschilden niet tussen patiënten met en zonder een infectie (15.8% versus 13.7%). Ongeveer 4/5 van alle patiënten (met of zonder een infectie van het hoofd of de hals) werden behandeld met heparine in therapeutische dosering (82.5% en 83.7%, respectievelijk). Bij pa-tiënten met een infectie was er geen significant verschil tussen degenen (n=47) die wel en degenen die niet (n=10) werden behandeld met heparine in de frequentie van nieuwe intracerebrale bloedingen en een slechte klinische uitkomst. Uit deze gegevens blijkt dat nieuwe intracerebrale bloedingen vaker optraden bij patiënten met een infectie van het hoofd of de hals. Behandeling met heparine lijkt de kans

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op een intracerebrale bloeding of slechte uitkomst niet te beïnvloeden. Het aantal patiënten met een infectie was echter te klein om conclusies te trekken over de veiligheid van heparine bij volwassenen met CVT en een infectie van het hoofd of de hals.

In **hoofdstuk 9** onderzochten we de frequentie, de pathofysiologie en de bijbehorende klinische manifestaties van hydrocefalus bij patiënten met CVT, die werden gepresenteerd in het Academisch Medisch Centrum in Amsterdam in de periode van 2000 tot 2010. Veertien van de 92 patiënten met CVT had een hydrocefalus (15.2%). Patiënten met hydrocefalus hadden vaker focale neurologische uitvalsverschijnselen (85.7% versus 49.4%, p=0.02) en waren vaker comateus (42.9% versus 16.4%, p=0.06) in vergelijking met patiënten zonder hydrocefalus. Trombose van het diepe cerebrale veneuze systeem (64.3% versus 8.9%, p<0.001) en oedeem van de basale ganglia en thalami (64.3% versus 3.8%, p<0.001) kwamen vaker voor bij patiënten met hydrocefalus. Patiënten met hydrocefalus hadden een slechtere klinische uitkomst bij follow-up (modified Rankin Scale score ≥2, 64.3% versus 32.4%, p=0.02) en overleden vaker (28.6% versus 9.3%, p=0.07). Dit onderzoek toont aan dat hydrocefalus vaker voorkomt bij CVT dan eerder werd gedacht, vooral bij patiënten met trombose van het diepe cerebrale veneuze systeem en oedeem van de basale ganglia en thalami. Het optreden van hydrocephalus bij deze patiënten is waarschijnlijk het gevolg van obstructie van het foramen van Monro door het hersenoedeem.

Hoofdstuk 10 beschrijft een prospectief onderzoek naar de werkzaamheid van een decompressieve hemicraniëctomie bij patiënten met een ernstige vorm van CVT. Een decompressieve hemicraniëctomie is een operatie waarbij een deel van de schedel (tijdelijk) wordt verwijderd, met als doel de hersenen meer ruimte te geven, zodat de zwelling door hersenoedeem en bloedingen niet leidt tot inklemming. Deze operatie werd in het Academisch Medisch Centrum in de periode van 2006 tot 2011 bij 10 patiënten met een ernstige vorm van CVT verricht. De gemiddelde leeftijd van de patiënten was 41 jaar (range 26–52). Vijf patiënten waren in coma voorafgaand aan de operatie. Alle patiënten op één na hadden een ruimte innemend hemorragisch veneus infarct. De mediane preoperatieve hersenverplaatsing was 9 mm (range 3–14). Twee patiënten overleden na de operatie aan progressief hersenoedeem en uitbreiding van de hemorragische veneuze infarcten. Van de overige 8 patiënten hadden er 5 een goede klinische uitkomst (modified Rankin Scale score 0–1). Decompressieve hemicraniëctomie bij ernstige CVT met dreigende inklemming kan levensreddend zijn en kan leiden tot een uitstekende klinische uitkomst.

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CONTRIBUTING AUTHORS

- Aramideh M, Department of Neurology, Medical Centre Alkmaar, The Netherlands.
- Arnold M, Department of Neurology, Inselspital Hospital University, Bern, Switzerland.
- Barinagarrementeria F, Department of Neurology, Instituto Nacional de Neurologia y Neurocirurgia, México City, Mexico.
- Berg R van den, Department of Radiology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Biemond BJ, Department of Haematology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Bousser MG, Department of Neurology, Hôpital Lariboisière, Paris, France.
- Broeg-Morvay A, Department of Neurology, Inselspital Hospital University, Bern, Switzerland.
- Canhão P, Department of Neurology, Hospital Santa Maria, Lisboa, Portugal.
- Cannegieter SC, Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands.
- Coert BA, Department of Neurosurgery, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Cornelissen JJ, Department of Haematology, Erasmus MC–Daniel den Hoed, Rotterdam, The Netherlands.
- Coutinho JM, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Dikstaal AA, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Ferro JM, Department of Neurology, Hospital Santa Maria, Lisboa, Portugal.
- Gaartman AE, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Haapaniemi E, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland.
- Heldner MR, Department of Neurology, Inselspital Hospital University, Bern, Switzerland.
- Hiltunen S, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland.
- Holt B van der, HOVON Data Centre, Erasmus MC Cancer Institute–Clinical Trial Centre, Rotterdam, The Netherlands.
- Kruyt ND, Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.

A

- Lauw MN, Department of Haematology, Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Majoie CBLM, Department of Radiology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Meisterernst J, Department of Neurology, Inselspital Hospital University, Bern, Switzerland.
- Meulendijks ER, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Middeldorp S, Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Munckhof P van den, Department of Neurosurgery, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Nemeth B, Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands.
- Peters GM, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Putaala J, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland.
- Silvis SM, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Stam J, Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands.
- Tatlisumak T, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden.
- Troost D, Department of Pathology, Academic Medical Centre, University of Amsterdam, The Netherlands.

RESEARCH PORTFOLIO

Name PhD student: Susanna Maria Zuurbier
PhD period: January 2011 – October 2016
Name PhD supervisor: Prof. dr. J. Stam and dr. J. Coutinho

1. PhD training	Year	Workload (Hours/ECTS)
General courses		
Basic Course Legislation and Organization for Clinical Researchers (BROK)	2011	0.9
Practical Biostatistics	2011	1.1
Clinical Epidemiology	2011	0.6
Systematic Reviews	2012	0.7
Advanced Topics in Biostatistics	2012	2.1
Scientific writing in English for Publication	2012	1.5
Specific courses		
Advanced Course in Thrombosis & Hemostasis, Cascais, Portugal	2011	1.0
17th European Stroke Organisation Summer School, Perugia, Italy	2013	1.0
3th ESO ESMINT ESNR Stroke Winter School, Bern, Switzerland	2016	1.0
Seminars, workshops and master classes		
Neurology Department Seminars, weekly	2011–2016	8.0
Neurology Journal Club, weekly	2013–2015	4.0
Presentations		
Oral presentation, Wetenschappelijke vergadering Nederlandse Neurovasculaire Werkgroep	2011	0.5
Oral presentation, Wetenschappelijke vergadering Nederlandse Vereniging voor Neurologie	2011	0.5
Oral and poster presentations, 20th European Stroke Conference, Hamburg, Germany	2011	1.0
Poster presentation, Wetenschappelijke vergadering Nederlandse Neurovasculaire Werkgroep	2012	0.5

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1. PhD training	Year	Workload (Hours/ECTS)
Presentations *(continued)*		
Poster presentations, 21th European Stroke Conference, Lisbon, Portugal	2012	1.0
Poster presentation, Wetenschappelijke vergadering Nederlandse Vereniging voor Neurologie	2012	0.5
Poster presentations, 22th European Stroke Conference, London, England	2013	1.0
Poster presentation, Wetenschappelijke vergadering Nederlandse Neurovasculaire Werkgroep	2013	0.5
Poster presentations, 23th European Stroke Conference, Nice, France	2014	1.0
Oral and poster presentations, 1st European Stroke Organisation Conference, Glasgow, England	2015	1.0
Oral presentation, Wetenschappelijke vergadering Nederlandse Neurovasculaire Werkgroep	2015	0.5
Oral and poster presentations, 2nd European Stroke Organisation Conference, Barcelona, Spain	2016	1.0
(Inter) national conferences		
International and Academic Research Conference, Manchester, England	2011	0.3
8th Conference Course of the Dutch Society of Neuroradiology, Amsterdam, The Netherlands	2012	0.3
International Society on Thrombosis and Haemostasis (ISTH), Amsterdam, The Netherlands	2013	1.0
Other		
• Member of Nederlandse Neurovasculaire Werkgroep	2011–2016	
• Junior Member of the European Stroke Organisation	2012–2016	
• Investigator of the TO-ACT (Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis) trial, an international randomized clinical trial on the efficacy and safety of endovascular thrombolysis for patients with a severe form of CVT	2011–2016	
• Investigator of the D-dimer and Factor XIII activation peptide in CVT study, an international prospective cohort study on the value of various biomarkers in the diagnosis of CVT	2011–2016	
• Local investigator of the DECOMPRESS-2 study, an international prospective cohort study on decompressive hemicraniectomy for patients with CVT	2011–2016	

1. PhD training	Year	Workload (Hours/ECTS)
Other *(continued)*		
• Member of the BEAST (Biorepository to Establish the Aetiology of Sinovenous Thrombosis) study group, an international collaboration to identify genetic mutations associated with CVT	2012–2016	
• Member of the CVIS (CVT Imaging Study) group, an international collaboration to examine if the Hounsfield unit/hematocrit ratio can be used to establish CVT on an unenhanced CT scan of the brain	2014–2016	
• Local investigator of the EXCOA (The benefit of EXtending oral antiCOAgulant treatment after acute CVT) study, an international cluster randomized trial on short- or long-term anticoagulation after CVT	2014–2016	
• Investigator of the TCCS (Transcranial color-coded duplex sonography in patients with CVT) study, a prospective study to evaluate the feasibility and time-course of the pulsatile index in patients with CVT	2015–2016	
• Local investigator of the RE-SPECT trial, an international randomized clinical trial on the efficacy and safety of dabigatran versus warfarin in patients with CVT	2015–2016	

2. Teaching	Year	
Lecturing		
Cerebral Venous Thrombosis, Neurologist and physician training	2011–2013	1.0
Cerebrovascular and Cerebral Venous Thrombosis, Neurology nurse training	2015–2016	0.5
Tutoring, mentoring, and supervising		
Neurological physical examination training of medical students	2011–2012	0.4
Tutoring and mentoring 10 medical students in cerebral venous thrombosis projects	2012–2016	8.0
Bachelor thesis Medicine, A. van Dissel	2011–2012	1.0
Bachelor thesis Medicine, A. Dikstaal	2015–2016	1.0
Other		
Author of various guidelines, Department of Neurology, Amsterdam	2013–2016	1.0

3. Parameters of Esteem	Year	
Grants		
Dutch Heart Foundation, Travel and Visit Grant	2011	

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PUBLICATIONS BY THE AUTHOR

International

1. Zuurbier SM, Coutinho JM, Majoie CB, Coert BA, van den Munckhof P, Stam J. Decompressive hemicraniectomy in severe cerebral venous thrombosis: A prospective case series. *J Neurol*. 2012;259:1099-1105.

2. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: A cross-sectional study. *Stroke*. 2012;43:3375-3377.

3. Stam J, Zuurbier SM, Coutinho JM. Local thrombolysis for severe cerebral venous sinus thrombosis. *Am J Roentgenol*. 2012;199:W531.

4. Coutinho JM, van den Berg R, Zuurbier SM, Majoie CB, Stam J. Mechanical thrombectomy cannot be considered as first-line treatment for cerebral venous thrombosis. *J Neurointerv Surg*. 2013;5:621-622.

5. Coutinho JM, Ferro JM, Zuurbier SM, Mink MS, Canhao P, Crassard I, Majoie CB, Reekers JA, Houdart E, de Haan RJ, Bousser MG, Stam J. Thrombolysis or anticoagulation for cerebral venous thrombosis: Rationale and design of the to-act trial. *Int J Stroke*. 2013;8:135-140.

6. Coutinho JM, van den Berg R, Zuurbier SM, VanBavel E, Troost D, Majoie CB, Stam J. Small juxtacortical hemorrhages in cerebral venous thrombosis. *Ann Neurol*. 2014;75:908-916.

7. Coutinho JM, Zuurbier SM, Stam J. Declining mortality in cerebral venous thrombosis: A systematic review. *Stroke*. 2014;45:1338-1341.

8. Siddiqui FM, Banerjee C, Zuurbier SM, Hao Q, Ahn C, Pride GL, Wasay M, Majoie CB, Liebeskind D, Johnson M, Stam J. Mechanical thrombectomy versus intrasinus thrombolysis for cerebral venous sinus thrombosis: A non-randomized comparison. *Interv Neuroradiol*. 2014;20:336-344.

9. Coutinho JM, Gerritsma JJ, Zuurbier SM, Stam J. Isolated cortical vein thrombosis: Systematic review of case reports and case series. *Stroke*. 2014;45:1836-1838.

10. Coutinho JM, Zuurbier SM, Gaartman AE, Dikstaal AA, Stam J, Middeldorp S, Cannegieter SC. Association between anemia and cerebral venous thrombosis: Case-control study. *Stroke*. 2015;46:2735-2740.

11. Zuurbier SM, van den Berg R, Troost D, Majoie CB, Stam J, Coutinho JM. Hydrocephalus in cerebral venous thrombosis. *J Neurol*. 2015;262:931-937.

12. Siddiqui FM, Dandapat S, Banerjee C, Zuurbier SM, Johnson M, Stam J, Coutinho JM. Mechanical thrombectomy in cerebral venous thrombosis: Systematic review of 185 cases. *Stroke*. 2015;46:1263-1268.

13. Zuurbier SM, Lauw MN, Coutinho JM, Majoie CB, van der Holt B, Cornelissen JJ, Middeldorp S, Biemond BJ, Stam J. Clinical course of cerebral venous thrombosis in adult acute lymphoblastic leukemia. *J Stroke Cerebrovasc Dis*. 2015;24:1679-1684.

14. Zuurbier SM, Hiltunen S, Tatlisumak T, Peters GM, Silvis SM, Haapaniemi E, Kruyt ND, Putaala J, Coutinho JM. Admission hypergly-

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cemia and clinical outcome in cerebral venous thrombosis. *Stroke*. 2016;47:390–396.

15. Zuurbier SM, Middeldorp S, Stam J, Coutinho JM. Sex differences in cerebral venous thrombosis: A systematic analysis of a shift over time. *Int J Stroke*. 2016;11:164–170.

16. Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MJ, Meisterernst J, Nemeth B, Meulendijks ER, Stam J, Cannegieter SC, Coutinho JM. The risk of cerebral venous thrombosis in obese women. *JAMA Neurology. 2016;73:579–584.*

17. Silvis SM, Middeldorp S, Zuurbier SM, Cannegieter SC, Coutinho JM. Risk factors for cerebral venous thrombosis. *Semin Thromb Hemost*. 2016.

18. Zuurbier SM, Coutinho JM. Response to letter regarding article, "Admission hyperglycemia and clinical outcome in cerebral venous thrombosis" *Stroke*. 2016, 47:e171.

19. Zuurbier SM, Coutinho JM, Stam J, Canhão P, Barinagarrementeria F, Bousser MG, Ferro JM, ISCVT Investigators. Clinical outcome of anticoagulant treatment in head or neck infection–associated cerebral venous thrombosis. *Stroke*. 2016;47:1271–1277.

20. Cotlarciuc I, Marjot T, Khan MS, Hiltunen S, Haapaniemi E, Metso TM, Putaala J, Zuurbier SM, Brouwer MC, Passamonti SM, Bucciarelli P, Pappalardo E, Costa P, Colombi M, Canhão P, Tkach A, Santacroce R, Margaglione M, Favuzzi G, Grandone E, Colaizzo D, Spengos K, Arauz A, Hodge A, Ditta R, Debette S, Pare G, Ferro JM, Thijs V, Pezzini A, Majersik JJ, Martinelli I, Coutinho JM, Tatlisumak T, Sharma P. Towards the genetic basis of cerebral venous thrombosis. The BEAST consortium: a study protocol. *Submitted*.

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Zuurbier SM, Coutinho JM, Majoie CB, Reekers JA, de Haan RJ, Stam J. Endovasculaire trombolyse bij cerebrale veneuze sinustrombose. *Tijdschrift voor Neurologie en Neurochirurgie*. 2012;113:11–16.

Zuurbier SM, Vermeer SE, Hilkens PHE, Algra A, Roos YBWEM. Secundaire preventie met clopidogrel na TIA of herseninfarct. *Nederlands Tijdschrift voor Geneeskunde*. 2013;157:A6221.

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Zuurbier SM, Coutinho JM. Cerebral Venous Thrombosis. In: Islam S, ed. Thrombosis and Embolism: from Research to Clinical Practice. 1st Ed. Springer International Publishing, 2016;183-194.

ABOUT THE AUTHOR

Yvonne (Susanna Maria) Zuurbier was born on May 18th 1982 in Wognum, the Netherlands. In 1999 she graduated from secondary school at the Oscar Romero in Hoorn. Before starting her medical studies at the Academic Medical Center, University of Amsterdam, she followed a Bachelor of Health Physiotherapy at the Amsterdam University of Applied Sciences. After 3 years, she started her medical studies at the Academic Medical Center, University of Amsterdam. She completed her 1st year of medical studies with honors in 2003. After completing her Bachelor of Health Physiotherapy with honors in 2004, she continued her medical studies. She obtained her Master degree with honors in 2007 and her Medical degree in 2009. Subsequently, Yvonne Zuurbier started working as a neurology resident at Tergooi hospital in Blaricum. In 2011 she started as a PhD candidate at the Department of Neurology at the Academic Medical Center, supported by a grant from the Dutch Heart Foundation. In 2013 she started her residency in Neurology at the Academic Medical Center (prof. dr. J. Stam, prof. dr. Y.B.W.E.M. Roos, dr. J.H.T.M. Koelman and prof. dr. I.N. van Schaik), which she hopes to successfully complete in 2018.

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