Cerebral Venous Thrombosis (CVT): Long-Term Vocational Outcome Study

Degree project thesis in Medicine

Erik Lindgren

Turgut Tatlisumak
Katarina Jood

Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden AND
Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

UNIVERSITY OF GOTHENBURG

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Abbreviations

APC – Active Protein C

CI – Confidence Interval

CNS – Central Nervous System

CT – Computed Tomography

CVT- Cerebral Venous Thrombosis

DAVF – Dural Arteriovenous Fistula

D-FIS – Daily Fatigue Impact Scale

DRVV – Dilute Russell Viper Venom Test

EQ-5D – Euro Quality of life -5 Dimensions

GCS – Glasgow Coma Scale

HAD – Hospital Anxiety and Depression Scale

HR – Hazard Ratio

ICH – Intracerebral Hemorrhage

ISCVT – International Study on Cerebral Vein and Dural Sinus Thrombosis

Lisat-11 – Life satisfaction 11

MRI – Magnetic Resonance Imaging

mRS – modified Rankin Scale

NIHSS – National Institutes of Health Stroke Scale

OR – Odds Ratio

SD – Standard Deviation

SIS – Stroke Impact Scale

Abstract

Title: Cerebral Venous Thrombosis (CVT): Long-Term Vocational Outcome Study

Author, year: Erik Lindgren, 2016

Institution, city, country: Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden AND Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Background: Cerebral venous thrombosis (CVT) is an uncommon form of stroke mainly affecting working aged individuals and predominantly females. Long-term consequences and outcomes of CVT are not well described.

Aim: To investigate long-term functional outcome in patients with CVT in terms of vocational activity.

Methods: All CVT patients diagnosed and treated in the Sahlgrenska University Hospital between 1997 and 2015 were retrospectively investigated through medical records. Surviving patients fulfilling the study criteria were invited to a clinical long-term follow-up visit.

Results: Of 90 survivors at working-age, 39 were followed-up (mean onset age 39 y, 62 % female). At the end of follow-up (median 134 months), 55 % of patients were fully recovered (modified Rankin scale, [mRS] =0-1), whereas 16 % reported significant disabilities (mRS=3-5). Most frequent residual symptoms were concentration or memory disorder (62 %), severe headaches (39 %), psychiatric problems (35 %), and fatigue (29 %). One quarter (28 %) was not able to return to work; following consequences from their CVT. Age and sex adjusted predictors for work return were absence of acute infarction (Hazard Ratio [HR]=3.8), absence of acute intracranial event (HR=2.5), oral contraceptive use among females (HR=3.3), straight sinus thrombosis (HR=3.5) and male sex (HR=3.3).

Conclusions: Long-term CVT residual symptoms seem to have negative impact on working life. Individual predictors for work return were absence of acute infarction, absence of acute

intracranial event, oral contraceptive use among females, straight sinus thrombosis and male sex.

Key Words: Intracranial Thrombosis, Outcome, Prognosis.

Background

Anatomy

Venous capillaries draining the brain assemble in venules inside the parenchyma. Cortical veins upon the cerebellar convexity, empties in bridging veins and pass through the subarachnoid room on their way to the sinus durae matris, consisting of one periosteal and one dural layer. The superior sagittal sinus and the inferior sagittal sinus drain the superficial and the deep venous system, respectively (Fig. I). Deep cerebral veins drain anteriorly to the cavernous sinus, or posteriorly via vein of Galen, joins with the inferior sagittal sinus into the straight sinus, which further drains into confluence of sinuses. Transverse sinuses are formed bilaterally, following posterior cranial fossa, forming sigmoid sinuses on each side, leaving the intracranial space as the internal jugular veins. The cavernous sinus is a venous plexus located superiorly to Sella Turcica, with a close connection to important anatomical structures such as the internal carotid, oculomotor-, trochlear-, ophthalmic-, and the abducens nerve. Vein of Trolard (superior anastomotic vein) between superior sagittal sinus and the superficial medial cerebral vein in the Sylvian fissure, and vein of Labbé (inferior anastomotic vein) between the superficial medial cerebral vein and the sigmoid sinus, facilitate alternative paths in case of vein occlusion (1).

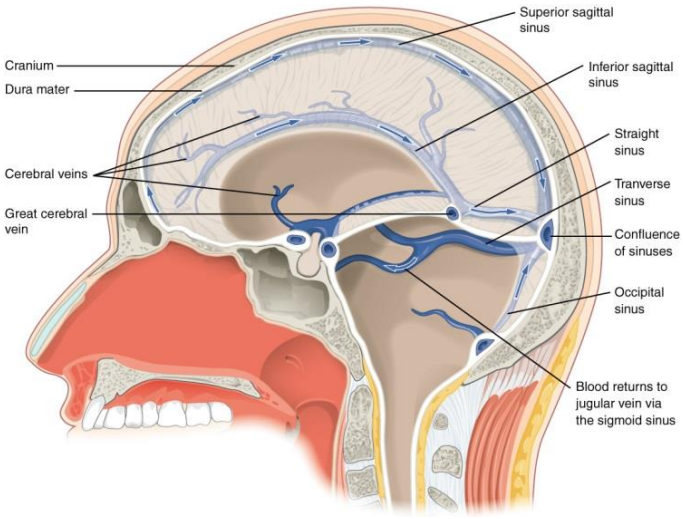

Figure I. *Anatomy of cerebral dural sinuses and veins (63).*

Pathogenesis

Symptoms and signs of sinus thrombosis can be divided into two main groups depending on whether the cause is thrombosis in cerebral veins - causing local effects, or thrombosis in

major sinuses - causing intracranial hypertension (Fig. II). Frequently, both mechanisms occur simultaneously.

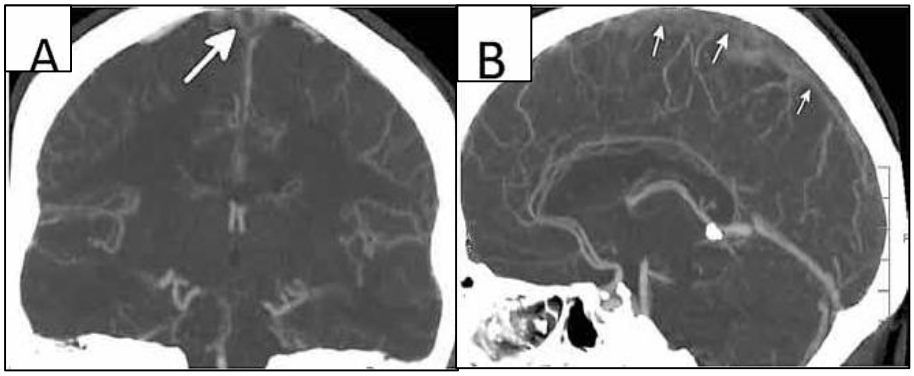

Figure II. *Enhanced computerized tomography on thrombosed superior sagittal sinus: A) Axial view, B) Sagittal view (64).*

Occlusion of cerebral veins leads to obstruction of venous blood flow and can cause hyperemia, localized edema or even brain infarction. Depending on individual anatomy and location of the occlusion, collateral veins may decrease the amount of damage caused. Cytotoxic edema is caused by ischemia, leading to intracellular swelling. Vasogenic edema is formed by eruption of the blood-brain barrier, leading to leakage of blood plasma and may cause brain tissue damage. The latter is reversible by treating underlying condition (2-4). Normally, cerebrospinal fluid is transported from the subarachnoid space through arachnoid villi into the superior sagittal sinus. Thrombus formed in the large venous channels may obstruct the venous outflow and block transport of cerebrospinal fluid from the subarachnoid space to the blood, and thereby cause increased intracerebral pressure (2, 3).

Historical Perspective

Cerebral venous thrombosis (CVT) was first recognized in 1825, by a French physician, Dr. M.F Ribes, describing a patient presenting with severe headache and seizure, as a cause of thrombosed superior sagittal and lateral sinuses (5). A few years later, the English physician John Abercrombie published a case report on a 24-year old woman developing headaches and seizures during her puerperium. Later, she died from status epilepticus. Autopsy revealed a thrombosis of the superior sagittal sinus and cortical veins (6). Confirmation of diagnosis has

changed over time and currently relies on radiological imaging of the dural sinuses and cerebral veins (7). The largest prospective study on CVT so far is the International Study on Cerebral Venous and Dural Thrombosis (ISCVT). From May 1998 to May 2001, 624 patients were included with a median follow-up of 16 months. Primary outcomes were death and dependency assessed by the modified Rankin Scale (8).

Epidemiology

Cerebral venous thrombosis is a fairly uncommon disease, believed to account for 0.5-1 % of all strokes, but the correct incidence is uncertain (2, 9). Early studies based on autopsy series suggest an incidence of 0.1-0.2/100.000 years, based on a prevalence of CVT of 9.3 % among 182 consecutive patients (10, 11). In a nation-wide study from Portugal based on investigations from late 1990:s, the incidence was 0.22/100.000/year (12). A cross-sectional study from the Netherlands reported an incidence of 1.32/100.000/year (13). However, improvements in radiological techniques allow less severe cases to be detected and may not only explain the increase in incidence, but also main part of the steady decrease in case fatality. A meta-analysis showed decreased case fatality from studies published prior to the millennium shift, whereafter the curve stabilized around 5-10 % (14). The case fatality is relatively lower than in other strokes, but the CVT patients are significantly younger. In the ISCVT, 78 % of CVT cases occurred in patients <50 years of age (8), compared to stroke in general where merely 31 % of the cases occur in patients younger than 65 years (15). Mean age among adults is 39 years (12). What furthermore differs from arterial stroke is the distribution between sexes. CVT is significantly more prevalent among women than men (16).

Risk Factors and Etiology

Predisposing causes to CVT are multiple and often combined (17). In the ISCVT cohort, 43.6 % had more than one known risk factor (Table I) (8). Virchow's triad (Fig. III) with decreased blood flow, vessel damage or disease, and relative hypercoagulation, are all important considerations in etiologic studies. Risk factors are usually divided into two major groups: acquired- and genetic risks. Coagulopathies with increased risk of extracerebral venous thrombosis have been reported to increase risk for CVT as well (18).

Prothrombotic Conditions

Risk factors frequently associated with CVT are miscellaneous prothrombotic conditions. In the ISCVT cohort with 624 patients, 34 % had inherited or acquired prothrombotic conditions (8), slightly higher occurrence than in an American study, reporting 21 % among 182 CVT case subjects (19).

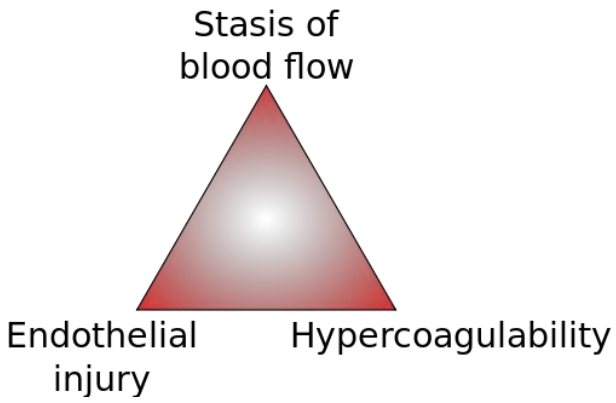

Figure III. *Virchow's triad - risk factors for venous thrombosis (65).*

Genetic Thrombophilia

A number of genetic factors predisposing for venous thrombosis have been found to be associated with CVT in small patient series; however, a full picture of the genetic backgrounds of the disease has not yet been explored. Affected individuals are particularly young, and therefore have low exposure to environmental factors, predicting a good chance of finding genetic markers associated to CVT.

Anticoagulation Protein Deficiencies

Antithrombin III-, protein C- and protein S deficiency, have been associated with CVT. Two comparable case-control studies with in total 172 CVT patients and 362 healthy control subjects, showed a combined odds ratio (OR) of 11.1 for protein C deficiency (95 %

Table I. *Causes and Risk Factors Associated with Cerebral Venous Sinus Thrombosis (2).*

Genetic prothrombic conditions
Antithrombin deficiency
Protein C and Protein S deficiency
Factor V Leiden mutation
Prothrombin mutation
Acuired prothrombic states
Nephrotic syndrome
Antiphospholipid syndrome
Homocysteinemia
Pregnancy
Puerperium
Infections
Otitis, mastoiditis, sinusitis
Meningitis
Systemic infectious disease
Inflammatory disease
Systemic lupus erytomatosus
Wegener´s granulomatosis
Sarcoidosis
Inflammatory bowel desease
Behcet´s syndrome
Hematologic conditions
Polycythemia, primary and secondary
Thrombocythemia
Leukemia
Anemia
Drugs
Oral contraceptives
Asparaginase
Mechanical causes, trauma
Head injury
Injury to jugular vein or cathetherization
Neurosurgical prochedures
Lumbar puncture
Miscellaneous
Dehydration
Cancer

confidence interval [CI] 1.87 to 66.05), and 12.5 for protein S deficiency (95% CI 1.45 to 107.29) (18, 20, 21).

Factor V Leiden Gene Mutation

The prothrombotic Factor V plays an important role in coagulation. Normally, the anticoagulant active Protein C (APC) inhibits and decomposes Factor Va. A certain mutation in Factor V, also internationally known as factor V Leiden mutation, modifies the binding site, causing a resistance to activated protein C and thereby a decrease of decomposition of Factor Va (22). A meta-analysis of 13 studies, including 469 CVT cases and 3023 control subjects, reported an association between Factor V Leiden mutation and CVT, (OR=3.38, 95 % CI 2.27 to 5.05) (18, 23). In Scandinavian countries, the prevalence of Factor V Leiden among general populations is 10-15 %. Factor V Leiden mutation is the most common genetic risk factor for thrombosis in general (22).

Prothrombin G20210A Mutation

A Guanine →Adenine transition in the prothrombin gene, slightly increase level of prothrombin, and is associated with CVT. The

prevalence is 2 % in a white population (24). A meta-analysis reported pooled OR of CVT of 9.27 (95 % CI 5.85 to 14.67) (23, 25).

Acquired Thrombophilia

Antiphospholipid and Anticardiolipin Antibodies, Hyperhomocysteinemia

Elevated levels of antiphospholipid and anticardiolipin antibodies have been associated with CVT in various studies, including ISCVT study where 5.9 % of the patients had increased levels (8). Hyperhomocysteinemia is a known risk factor for DVT, although not yet shown to increase risk of CVT.

Gender-Specific Risk Factors

In young women, particularly important from a CVT point of view, the most frequent risk factors are oral contraceptive use, pregnancy, and puerperium, all causing elevated levels of estrogen (8). Additional associated gender-specific risk factors are hormone replacement therapy, the day-after pill, and in vitro fertilization (26). As mentioned before, CVT is significantly more common among women than men. On the other hand, women with gender-specific risk factors have better prognosis – complete recovery (modified Rankin Scale [mRS] =0-1) 85 % after 6 months versus 71 % among men (8, 16).

Cancer

Hematological and solid malignancies seem to be associated with CVT. Preliminary data from an unpublished multicenter study predict increased risk of CVT in patients with cancer, compared to those without (OR=4.4, 95 % CI 3.2 to 6.2) (27). Theoretically, CVT can be caused by cancer in at least 3 different ways: 1) direct effect of the tumor – local meningioma or metastases could increase pressure, or grow into the sinuses, 2) coagulation disturbance, and 3) cancer treatment. In particular L-Asparaginase and intrathecal chemotherapy are highly suspected to be associated with CVT (22).

Infections

Infectious causes of CVT have declined in developed countries as antibiotic treatment improved. However, nervous system infections are likely to remain an important cause in developing countries. Nowadays local infections in the cranial area such as otitis, mastoiditis, and sinusitis, account for the majority of infectious etiology, generally causing the rare cavernous sinus thrombosis (28).

Other Causes

Other potential causes and conditions associated with CVT mainly in small case reports, are hematological diseases – polycythemia, thrombocythemia and anemia (7), inflammatory bowel disease, nephrotic syndrome and dehydration (8). Dural sinuses and veins are vulnerable and at risk during neurosurgical procedures and interventions. Cranial traumas could also cause damage to the cerebral venous sinuses. Intracranial hypotension could cause increased tension in meninges and thereby increase risk of clotting. Reports suggesting lumbar puncture as a risk factor, often consider intracranial hypotension as the cause (18). In the ISCVT population, no underlying risk factor was found in 12.5 % of the patients (8).

Clinical Manifestations and Diagnosis

Symptoms

CVT presents with a wide panorama of symptoms, ranging from isolated headache to coma. Most patients present with severe headache although other common baseline symptoms include nausea, seizures, severe focal neurological deficits, and altered consciousness. Furthermore, clinical onset differs from acute to subacute or even chronic. In the ISCVT patients, 37 % of onsets were acute (<48 hours), 56 % subacute (>48 hours to 30 days), and 7 % chronic (>30 days). Median delay from onset of symptoms to hospital admission was four days and onset to diagnosis seven days (8).

Table II. *Localization of cerebral venous thrombosis and its relationship with clinical symptoms (18).*

Location of Thrombosis	Characteristic Symptoms
Superior Sagittal Sinus	Headache, symptoms of increased intracranial pressure, papilledema
Lateral sinus thrombosis	Symptoms from middle ear infection, fever, ear discharge, pain in ear mastoid, increased intracranial pressure
Cortical involvement	Hemianopia, contralateral weakness, aphasia
Deep venous system	Thalamic or basal ganglia symptoms – rapid neurological deterioration, paraparesis, alteration in consciousness in the absence of focal findings. Bilateral brain involvement is not infrequent.

Clinical picture partly depends on the location and extent of thrombosis (Table II), age of the patient, presence of parenchymal lesions, and time to diagnosis. By grouping symptoms and signs, three syndromes are frequently identified and related to a specific medical condition: 1) isolated intracranial hypertension – headache, visual acuity defect, diplopia, and papilledema, 2) focal symptoms – neurological deficits or seizures, and 3) subacute diffuse encephalopathy – bilateral- or multifocal signs, delirium or dysexecutive disturbances. Less frequent syndromes include cavernous sinus syndrome, subarachnoid hemorrhage generalized or localized to cortical sulci, and syndromes of the lower cranial nerves, including multiple palsies (7).

A generalized headache is the most frequent symptom (Table III), often described as diffuse and progressive over days to weeks. A minority of patients present with thunderclap headache, resembling of subarachnoid hemorrhage. Headache was present in 90 % of adult patients in the ISCVT (8). Isolated headache without focal neurological symptoms or papilledema occurs in up to 25 % of patients with CVT. Another 25 % presents with headache in combination with papilledema or sixth nerve palsy (29). However, headache is a clearly non-specific symptom, and the vast majority of patients with isolated headache do not have CVT. Absence of headache is more common among relatively elderly patients, patients with malignancy, isolated cortical vein thrombosis, and among men (30).

Thirty to forty percent of patients present with intracranial hemorrhage (ICH). Parenchymal lesions and focal brain injuries often present with seizures or focal neurological deficits, mostly hemiparesis and aphasia (8, 31, 32). Forty percent of patients present with any type of motor or sensory deficits (8). Approximately 40 % of patients suffer from one or more seizures in the acute phase, either focal or generalized (8, 18).

Table III. Presenting symptoms and sinuses thrombosed in cerebral venous thrombosis (8).

Symptoms and signs	**%**
Headache	88.8
Visual Loss	13.2
Papilledema	28.3
Diplopia	13.5
Stupor or Coma	13.9
Aphasia	19.1
Mental Status Disorders	22.0
Left paresis	20.4
Right paresis	20.4
Any paresis	37.2
Bilateral motor signs	3.5
Focal seizure	19.6
Seizure with generalization	30.0
Any seizure	39.3
Sensory symptoms	5.4
Other focal cortical sign	3.4
Thrombosed sinus	**%**
Superior sagittal sinus	62.0
Lateral sinus, left	44.7
Lateral sinus, right	41.2
Straight sinus	18.0
Deep venous system	10.9
Cortical veins	17.1
Jugular veins	11.9
Cerebellar veins	0.3
Cavernous sinus	1.3

Diagnosis

D-dimer

Elevated D-dimer is associated with CVT, especially together with acute onset of symptoms and greater thrombus extension. However, there are many causes of elevated d-dimer, thus the role of D-dimer in diagnosis of CVT is limited. Low levels of D-dimer cannot exclude CVT suspicions, nevertheless, high levels can help identify patients with low probability of CVT (33).

Radiology and Location

Diagnosis of CVT requires visualization of the thrombus, in combination with insufficient flow in the dural sinuses or cerebral veins. Direct signs include cord sign, delta sign and with contrast the empty delta sign of dural sinuses (Fig. IV). The most common indirect signs are ICH and localized cerebral edema. Venous hemorrhagic infarction and juxtacortical hemorrhage are both associated with CVT. The latter is strictly associated with thrombus in

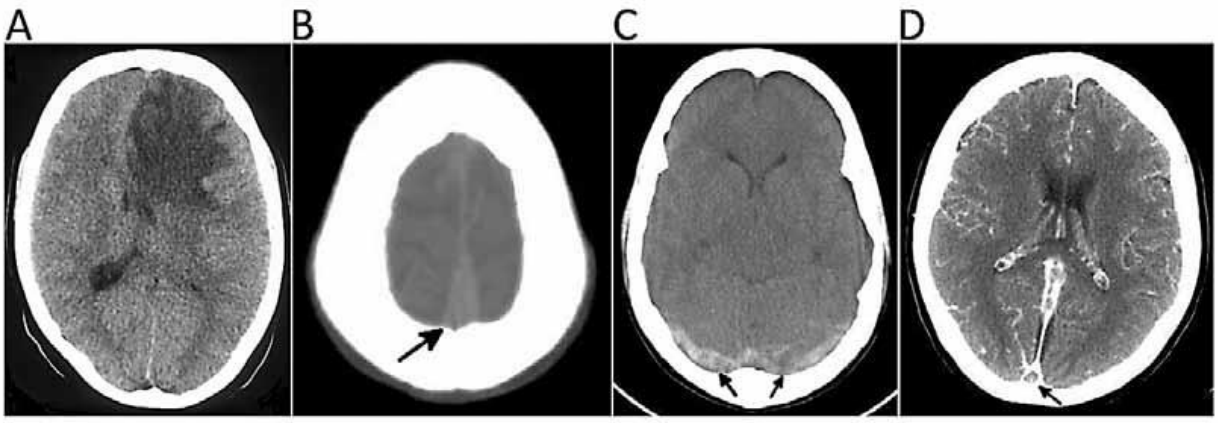

Figure IV. *Computed tomography findings on sinus thrombosis A) Venous infarction with midline shift as a cause of major superior sagittal sinus thrombosis. B) Dense clot sign, here indicative of superior sagittal sinus thrombosis. C) Dense clot sign in transverse sinuses bilaterally. D) Empty delta sign where contrast leaves out an empty ring at site of thrombus (64).*

the superior sagittal sinus (32). In case of ICH of unclear origin, or cerebral infarction over typical arterial areas – imaging of the venous system is recommended (18).

There are essentially three imaging techniques to diagnose CVT: Magnetic Resonance Imaging (MRI) with MR-venography (MRV), computed tomography (CT) with CT-venography, and catheter angiography (18). Most sensitive is the MRI in combination with MRV. Frequently used are time-of flight sequences measuring venous flow, and contrast enhanced MRV. Absence of flow void (no-flow phenomenon) in combination with variation in signal within the sinus or vessel, are major early signs for CVT. Imaging signal may differ depending on the age of the thrombus. Disadvantages are lack of availability, risk of motion artifacts, and long examination time (3).

Unenhanced CT often displays pictures without findings indicative of CVT and merely detects approximately 30 % of cases. Such findings could be hyperdensity of a dural sinus or cortical vein, in posterior part of superior sagittal sinus appearing as a delta- or filled delta

sign. Anatomic variations of the dural sinuses further complicate the diagnosis, resulting in insufficient sensitivity for CT in absence of contrast. However, plain CT has its place in excluding tumor, subdural hematoma, or abscess (9, 34).

CT-venography with contrast is a faster and less expensive alternative to MRV, yet more sensitive than unenhanced CT. Bone artifacts from the cortical bone may interfere with imaging of the sinus. Diagnostic difficulties may occur in confirming the thrombus during the first days after onset. However, as a result of the complicated presentation, patients often present in a subacute or chronic manner, making CT-venography an important diagnostic tool. Overall accuracy of combined CT and CT-venography is 90-100 %, and considered equal to MRV in diagnostic power of CVT (18).

As radiological imaging techniques improve, CVT diagnosis become less dependent on invasive methods. In cases with still uncertain diagnosis after CT-venography or MRI, cerebral angiography may be indicated. Cortical veins and variations in deep venous structures may be hard to visualize with CTV and MRV. In these cases, cerebral angiographies still play an important role, despite being more invasive. Positive findings include insufficient, delayed or failure of cerebral sinus and vein appearance. Cerebral angiography is a prerequisite for endovascular procedures (18).

Treatment

Independently of type of stroke, organized stroke care has shown great beneficial effects in the acute care. Studies stating, inter alia, 14 % reduction in odds of death at one year (OR=0.86, 95 % CI 0.76 to 0.98), death or institutionalization (OR=0.82, 95 % CI 0.73 to 0.92) and death or dependency (OR=0.82, 95 % CI 0.73 to 0.92) (35, 36).

Primary treatment with low molecular heparin has limited evidence from randomized clinical trials; however, hemorrhagic complications during anticoagulation with heparins are low or even non-existing (37-39). Immediate heparin treatment is recommended by international guidelines (18, 40). Low molecular-weight heparin has better safety profile and is generally preferred over unfractioned heparin, except in cases at risk for neurosurgical intervention where rapid reversal of anticoagulation may be necessary (3, 41, 42).

For cases deteriorating despite proper anticoagulant treatment, local thrombolysis and mechanical extraction of thrombotic material may be considered. These recommendations are based upon small case series and case reports, thus not suggested as standard treatment (18). Despite absence of randomized trials, decompressive hemicraniectomy has its place in patients at risk of transtentorial herniation, the most frequent cause of death in the acute stage of CVT. Management of intracranial pressure is vital in prevention of fatal consequences (43, 44).

A clinical presentation without seizures means low risk of seizures occurring during the course. In contrast, patients presenting with seizures have a high risk of recurrence, indicating use of preventive anticonvulsive drugs (45, 46).

Recurrence of extracranial thrombosis occurs in 4 % of patients and recurrence of CVT in 2 % of patients during the first year after diagnosis (8). In patients with transient risk factors, recommended treatment duration with vitamin K antagonists is 3 to 6 months. In patients with unprovoked CVT, recommended duration is 6 to12 months. Permanent anticoagulation is recommended in patients with severe thrombophilia or recurrent CVT. However, the optimal duration of treatment remains uncertain (18). Further use of contraceptives or other estrogen

is contraindicated. During pregnancies, subcutaneous treatment with low molecule weight heparin is indicated.

Outcome

Stroke outcome is often measured through the modified Rankin Scale (mRS) ranging from a score of 0 representing no symptoms at all, to the score of 6, representing death. A score >2 indicates functional dependence (App. I). Overall vital and functional prognosis in CVT is far better than arterial stroke. Short term functional outcome is considered good with 79 % of the patients achieving functional independency. Another 10 to 15 % of the patients remains dependent and requires help in their daily routine activities. In the ISCVT, 3.4 % died within 30 days (8, 47). However, higher case-fatality have been reported from Pakistan (6 %) (28), United States (13 %) (48) and Iran (15 %) (49). Few prospective studies have been performed describing long-term outcome, all measured with the mRS (8, 50, 51). In the ISCVT, risk factors for poor long-term prognosis were malignancy, thrombosis of the deep venous system, intracranial hemorrhage on admission, Glasgow Coma Scale <9, mental status disturbance, age >37, male sex and central nervous system infection (8). A recent study additionally suggests high admission glycaemia being a predictor for poor clinical outcome (52). A retrospective study conducted in Helsinki, Finland by Hiltunen et al. (n=161, median follow up time 39 months) reports good clinical long-term outcome with 81 % scoring 0-1 on the mRS. In contrast, only 57 % had returned to work at end of follow up (53). Mental depression, anxiety, cognitive deficits and/or concentration impairments are present in approximately half of CVT patients and appear to have negative impact on psychosocial and employment status (53-55). Long-term functional outcome after CVT may be considered good when measured with mRS, however, long-term functional outcome regarding working ability, cognitive dysfunction, headache, and depression rate after CVT, remains poorly investigated.

Aims

Primary aim of this study was to investigate long-term functional outcome in terms of return to work, dependency in activities of daily living, and residual symptoms in patients with CVT.

Secondary aim was to investigate etiological-, clinical-, radiological-, laboratorial- and genetic characteristics of adult patients with diagnosis of CVT, admitted to the Sahlgrenska University Hospital, Gothenburg, with onset between 1997-01-01 and 2015-01-01.

Methods

All patients between 1997 and 2015 with a verified diagnose of CVT, admitted to the Sahlgrenska University Hospital, were searched for in the Sahlgrenska University Hospital Patient Administrative Databank, using the codes of diagnosis for CVT; ICD-9: 1.4376A (Nonpyogenic thrombosis of intracranial venous sinus), ICD-10: I63.6 (Cerebral infarction due to cerebral venous thrombosis, nonpyogenic), I67.6 (Nonpyogenic thrombosis of intracranial venous system), O87.3 (Cerebral venous thrombosis during puerperium) and O.22.5 (Cerebral venous thrombosis during pregnancy). It was predicted to find approximately 10 patients each year. Therefore, the aim was to include 150 patients, considering that some patients could not be reached, and some would not wish to participate. Patients with onset earlier than 1997-01-01 or later than 2015-01-01 were excluded together with cases in whom the diagnosis could not be verified according to medical journal, patients with onset age younger than 18 years as well as duplicate registrations.

Part 1 – Baseline

Remaining patients were considered eligible to the first part of the study where baseline characteristics were investigated. Medical records were reviewed to gather demographics, risk factors, clinical features, radiological imaging, laboratory findings, complications, and similar relevant information. The data were entered to a SPSS-based database. Altogether, 150

variables were registered on each patient. Baseline information included: gender, medication, educational level, employment status, previous and current diseases, in particular previous thrombosis, malignancy, polycythemia vera, essential thrombocythemia, vasculitis, inflammatory bowel disease, chronic headaches, body weight, height, body mass index, known allergies, smoking, alcohol use, previous pregnancy, exposure of pregnancy, puerperium, systemic infection, local infection, mechanical trauma or surgery, oral contraceptive use, lumbar puncture, and hormone replacement therapy within the last 3 months preceding CVT onset. Family history of: CVT, other venous thrombotic disease, stroke and type of stroke. Presented symptoms of CVT were: headache - type, onset characteristics, progression, severity and location, nausea and vomiting. Seizure – focal, generalized or secondary generalized, seizure in acute phase. Neurological focal deficits - aphasia, paresis, mental state disturbance, observed papilledema and stiff neck. Onset clinical condition was also measured with Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS) and the mRS, constructed retrospectively (56, 57).

Radiological findings were gathered from radiological records, CT, CTV, MRI, MRV, and cerebral angiography, during the hospital stay. Some records were reviews on images from other hospitals concerning the current disease. In uncertain cases, the overall senior physicians' clinical and radiological assessments were considered liable. Data included confirmed thrombus in: transverse and sigmoid sinus bilaterally, jugular internal vein bilaterally, superior and inferior sagittal sinuses, straight sinus, confluence sinus, cavernous sinus, deep venous system, cortical and cerebellar veins. Total number of sinuses thrombosed was calculated and recorded. Presence of parenchymal lesions – hemorrhagic or non-hemorrhagic, infarctions, dural arteriovenous fistulas and subarachnoid hemorrhage were recorded. Laboratory records were reviewed in search for both acquired - Lupus

Anticoagulant (Dilute Russell Viper Venom Test, DRVV) and antiphospholipid antibodies, and genetic thrombophilia - factor V Leiden mutation, prothrombin G20210 A mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency. In hospital treatment was recorded as intravenous or subcutaneous anticoagulation, oral anticoagulation, antiepileptic drugs, local thrombolysis, decompressive craniectomy, hematoma evacuation, and other surgical procedure. Complications were defined as any event recorded as treatment complication in the medical journal or previously not confirmed bleeding. Outcome at discharge was recorded according to the mRS, NIHSS and GCS.

Part 2 – Long-Term Follow-Up

Patients aged over 63 years at onset were not included in the analysis of vocational outcome. Medical records in general do not contain specific data on employment and deceased patients were therefore also excluded. Patients living abroad were also excluded as they were expected to be difficult to reach. Remaining patients were sent a letter containing comprehensible information about the study and invitation to participation (App. II). Patients were given an opportunity to achieve additional information by phone and asked to return a written consent (App. III). Patients were informed about the possibility of breaking the agreement at any time during the study. Those who did not return the response letter were contacted by telephone to investigate whether the patients were willing to participate or not. Individuals not able to reach were excluded. After receiving confirmation of participation in the long-term functional outcome and/or genetic study, a postal questionnaire was sent including study-specific questions regarding headache, living- and working situation and a battery of validated instruments measuring outcome after stroke (Stroke Impact Scale [SIS]), depression (Hospital Anxiety and Depression Scale [HAD]), fatigue (the Daily Fatigue Impact Scale [D-FIS]), health-related quality of life (EQ-5D) and life satisfaction (Lisat-11) (App. IV). Patients also

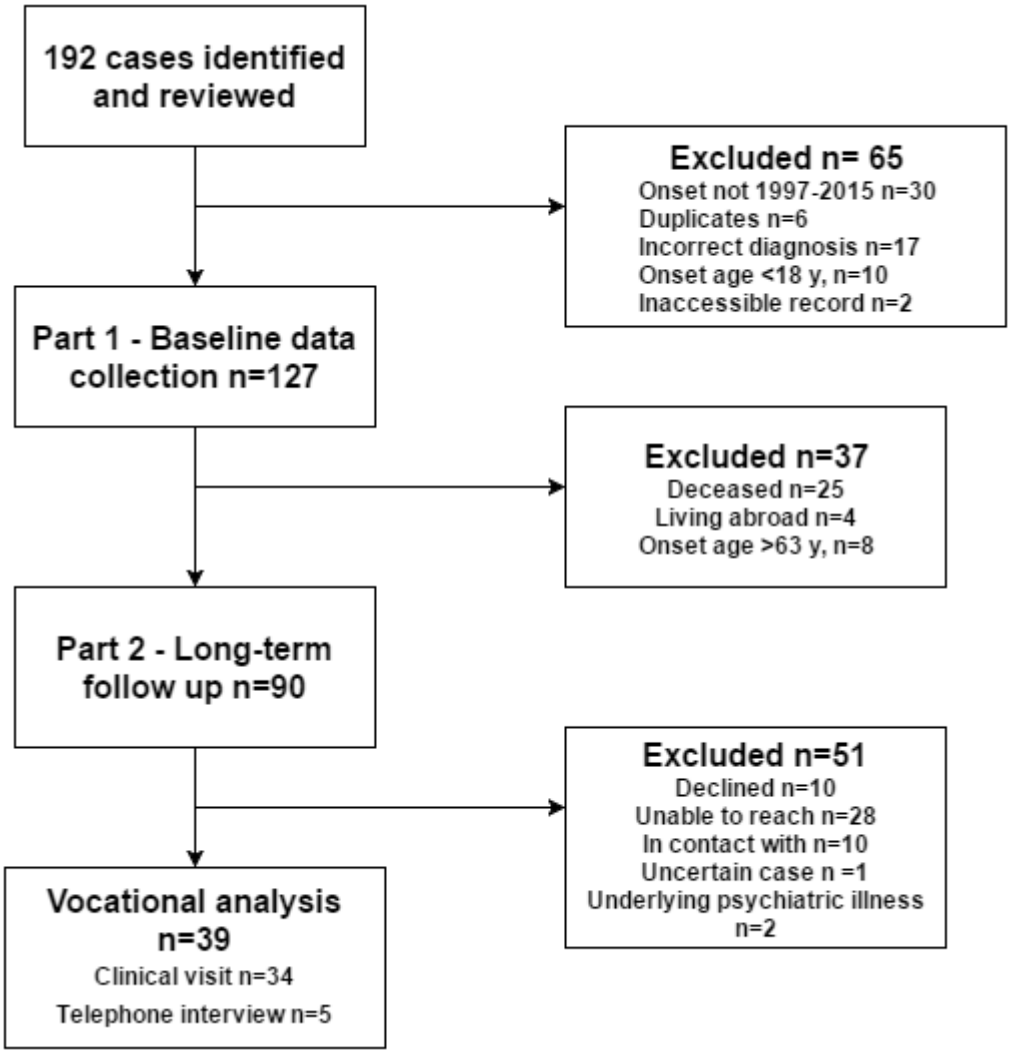

Figure V. *Flow chart on number of patients participating in Cerebral Venous Thrombosis (CVT): Long-Term Vocational Outcome Study.*

received an invitation to a clinical visit. In this report, results from questions regarding working situation is presented.

Patients, who were not able to take part in a clinical visit, were asked to return their forms by mail. As an alternative to the clinical visit, they were offered to be contacted by telephone. Patients who returned their questionnaires but did not participate in follow-up, were not included in the analysis of this report. Some patients were able to reach, but did not decide

whether they wanted to participate or not, and were also excluded. Reasons for not taking part in the clinical visit were living too far away or not being able to take time off from work. At follow-up, patients were given the opportunity to achieve additional information about the study face to face. Oral consent was documented in the medical record.

Clinical visits were conducted from 2016-03-11 to 2016-04-29 at the Sahlgrenska University Hospital including a detailed interview and neurological examination. The interview focused on the patient's current health condition, medication, complications post CVT (bleeding, recurrent venous thrombosis, hospitalization, miscarriage) and residual symptoms (headache, seizures, fatigue, concentration or memory disorder, visual problems, motor or sensory problems, speech disorders, spasticity, tremor, and dizziness) and CVT etiology (hematological/thrombotic disease, hormone-related, septic, mechanical/traumatic, malignancy, inflammatory disease, or cryptogenic. The interviews and examinations were conducted by the same physician, and standardized by a clinical questionnaire (App. I, V). The mRS, NIHSS, and Barthel Index (BI) scale were assessed. When applicable, missing baseline data was completed or clarified. Blood samples (10 ml) were collected by a licensed nurse, to be stored encrypted in a deep freezer at Sahlgrenska University Biobank, Gothenburg, for future genetic analyses.

Primary outcome measures were functional outcome. Work return within time to long-term follow-up, mRS score 0-1, NIHSS score 0-2 and BI score 100 were considered favorable outcome. Work return was defined as ≥50 % gainful work (100 %=40 hours/week) or equivalent activity such as studying.

Statistical Analyses

All statistical calculations were performed using IBM SPSS Statistics version 21. Collected data were compared and analyzed using quantitative descriptive statistic methods. Time to work return was calculated using Kaplan Meier. Cox regression analyses served to investigate independent factors associated with return to work within the follow-up period. Demographic factors, clinical findings, and radiological findings were considered possible explanations for patient outcome. Hazard ratio with 95 % CI was calculated individually on each variable. All p-values <0.10 in the univariable analysis were considered valuable to further analyses in the multivariable model. After adjusting for age and sex, a two-sided p-value <0.05 was considered significant. Based on clinical and theoretical experience, four variables were chosen to be put in an additional multivariable model; age >39 (median age in follow-up cohort), more than 2 risk factors, parenchymal- or subarachnoid hemorrhage and previous thrombosis. Chi square tests served to investigate association between residual symptoms at long-term follow-up and work return within the follow-up period.

Ethics

This study has been approved by the Regional Ethical Review Board in Gothenburg (2015-01-11, Dnr: 898-15) and was carried out in accordance with the Helsinki Declaration 1964. The study implied no physical risk for patients included. All data was processed encrypted to minimize the risk of privacy violation. Patients were given the possibility to discuss their disease with professional personnel, but the study meant no further medical benefits. A prerequisite for decent mortality and outcome analysis, were the inclusion of deceased individuals to baseline data collection. This data was necessary to avoid bias and skewed patient selection. Being considerate, we did not contact relatives of the deceased patients and collected data from their medical records only. In addition to the patients suffering a CVT, relatives are also affected. Increased knowledge about etiology, predictors and outcome, could

increase life quality not only for the patients but also for their relatives. The potential winning from this project can thus be considerable from a patient and family perspective. All participants' autonomy was respected and patients were informed about the possibility of withdrawing their consent at any time during the study. Personal data and blood samples would then have been erased and destroyed.

Results

Part 1 - Baseline Characteristics

One hundred twenty-seven patients fulfilled the criteria for participation in part 1 of the study. Gender distribution was 82 females (64.6 %) and 45 males (35.4 %). Mean age at onset of symptoms was 43.3 years (range 18 to 80, SD=16.3), women were slightly younger than men 42.1 years (range 18 to 69, SD=16.6) and 45.5 years (range 18 to 80, SD=15.7) respectively. Median onset to diagnosis was 6 days (Inter Quartile Range [IQR] 2 to 12). According to medical records, about one third of the patients were unemployed at onset (n=36, 30.2 %), among these, 14 (11.8 %) were retired due to old age, nine (7.6 %) on full-time sickness benefits, seven (5.8 %) on sick leave, three (2.5 %) on parental leave and three (2.5 %) job-seekers. Eighty-three patients (69.7 %) were considered employed, categorized as workers (n=70, 58.8 %) or students (n=13, 10.2 %). Further demographic, clinical and radiological features are described in Table IV.

Symptoms

Most frequent presenting symptom was headache (80.2 %), followed by nausea, any focal neurological deficits and vomiting. Clinical presentations were diverse, and multiple symptoms were not infrequent. Other important symptoms were any type of seizure, visual defect, decreased alertness as in GCS score 9-14 and mental state disturbance. Eight patients presented with coma.

Radiological Findings

Median number of sinuses thrombosed was 3.0 (IQR 2 to 4). The three most frequently occluded sinuses or veins were superior sagittal sinus, left lateral sinus and right lateral sinus. Upon first radiological examination, half or the patients had any parenchymal lesion (n=65, 52.8 %). The occurrences of hemorrhagic and non-hemorrhagic lesions were similar. During the acute hospital stay, infarction was confirmed in 52 patients (40.9 %). 57 patients (44.9 %) had any parenchymal hemorrhage and 21 patients (16.9 %) had subarachnoid hemorrhage. Among six patients (4.7 %), a dural arteriovenous fistula (DAF) was discovered.

Risk Factors and Etiology

Observed risk factors are summarized in Table IV. Genetic thrombophilia and systemic infection were the most common risk factors in the whole group, both present in 21 cases (16.5 %). Other critical risk factors were infection of the head area or CNS, found in 16 patients (12.6 %), malignancies or intracranial tumor 14 (11 %), hematological condition defined as polycythemia vera, essential thrombocythemia, or confirmed anemia 14 (11 %). Twelve patients (9.4 %) had a previous venous thrombotic event. Among women younger than 50 years, a majority used oral contraceptives (n=27, 51.9 %), 5 (9.4 %) were pregnant at onset and 6 (11.3 %) had given birth within 0-3 months prior to onset.

Table IV. Baseline data on 127 patients with Cerebral Venous Thrombosis (CVT).

	No. of cases	%	Missing data		No. of cases	%	Missing data
Female	82	64.6		***Gender Specific risk n=82***			
Mean onset age	43.3 y	(16.3)		Previous pregnancy*	46	61.3	7
Female	42.1 y	(16.6)		Hormone Replacement Therapy*	3	3.7	1
Male	45.5 y	(15.7)		Pregnancy 0-3 months **	11	20.8	
Presenting symptoms				Puerperium 0-3 months **	6	11.3	
Headache	101	80.2	1	Oral contraceptives**	27	51.9	1
Any seizure	35	27.8	1	***Occluded sinus/vein***			
Generalized	32	25.4	1	Superior sagittal sinus	63	50.0	1
Focal symptoms	60	47.2		Lateral sinus, left	60	47.6	1
Aphasia	19	15		Lateral sinus, right	59	46.8	1
Paresis	43	33.9		Straight sinus	28	22.2	1
Mental State Disturbance	25	19.7		Cortical veins	13	10.4	1
Visual defect	31	24.4		Deep venous system	5	4	1
Papilledema detected	14	11		Jugular veins	37	29.4	1
Nausea	65	51.2		Cavernous sinus	4	3.2	1
Vomiting	54	42.5		***Radiology Upon admission***			
Decreased alertness (GCS 9-14)	30	23.6		Any parenchymal lesion	65	52.8	4
Coma (GCS <9)	8	6.3		Hemorrhagic	44	35.8	4
Neck Stiffness	3	2.4		Non hemorrhagic	45	36.6	4
Risk factors and etiology				***Radiology during hospital stay***			
Previous thrombosis	12	9.4		Brain infarction	52	40.9	
Infection, systemic	21	16.5		Parenchymal hemorrhage	57	44.9	
Infection, local	16	12.6		Subarachnoid hemorrhage	21	16.9	3
Genetic thrombophilia	21	16.5		Dural Arteriovenous Fistula	6	4.7	
Cranial trauma	3	2.4	1	***Education onset***			22
Surgery	11	8.7		Lacking	1	1	
Lumbar puncture	2	1.6	1	Primary	5	4.8	
Dehydration	9	7.1		Secondary	62	59	
Malignancy/intracranial tumor	14	11		Tertiary	37	35.2	
Chronic headache disease	12	9.4		***Employment onset***			8
Smoking	13	16.7	49	Employed	83	69.7	
Hematological condition	14	11		Worker	70	58.8	
Severe Anemia	10	7.9		Student	13	10.2	
Essential Thrombocythemia	3	2.4		Unemployed	36	30.2	
Polycythemia Vera	1	0.8	2	Retired old age	14	11.8	
Vasculitis	0	0		Sickness benefits	9	7.6	
Inflammatory Bowel Disease	6	4.7		Sick leave	7	5.8	
Family history CVT	0	0	68	Parental leave	3	2.5	
Family history thrombosis	19	33.3	70	Job-seeker	3	2.5	

Data appear as n (%) or mean (Standard Deviation)
**Among females n=82*
*** Among females <50 y, n=53*
Y – years, GCS-Glasgow Coma Scale, CVT – Cerebral Venous Thrombosis

Treatment and Outcome at Discharge

Almost all patients received intravenous (IV) or subcutaneous (SC) anticoagulation treatment (n=118 patients, 93.7 %). Local thrombolysis was performed in 24 patients (18.9 %) out of which 10 (41.7 %) had no complication to the treatment. Bleeding occurred in six patients (25 %) and other complications as clinical worsening or new neurological symptoms in eight patients (33.3 %). In the group without local thrombolysis (n=103), 92 patients (89.3 %) had no complication. Bleeding occurred in six (5.8 %) and five (4.9 %) suffered from other complications. At discharge, 27 (21.3 %) patients had favorable outcome (mRS 0 to 1), 57 patients (44.9 %) were dependent or worse (mRS 3 to 6), out of which eight patients (6.3 %) died before leaving hospital (Table V). Complications to anticoagulation treatment in hospital are described in Table VI. Other treatments were decompressive craniectomy (n=9, 7.1 %), hematoma evacuation (n=6, 4.7 %), other surgery (n=14, 11.1 %) and anticonvulsive drugs including direct seizure preventing drugs as diazepam (n=39, 31 %).

Table V. *Outcome at discharge (n=127)*

Modified Rankin Scale	No. of cases	%
0	6	4.7
1	21	16.5
2	43	33.9
3	23	18.1
4	8	6.3
5	18	14.2
Death	8	6.3
Good early outcome (0-1)	27	21.3
Death or dependency (3-6)	57	44.9
NIHSS (1 missing)		
0-2	96	76.2
>2	18	14.3
Intubated or postictal state	4	3.1
Deceased	8	6.3
Glasgow Coma Scale		
3	8	6.3
4-8	4	3.1
9-14	2	1.6
15	113	89

NIHSS – National Institutes of Health Stroke Scale

Table VI. *Complications in hospital and different types of anticoagulation treatment among patients with cerebral venous thrombosis.*

	Complication in Hospital		Number of cases	%
Treatment - Intravenous or Subcutaneous Anticoagulation	Yes	No	95	80.5
		Bleeding	11	9.3
		Other	12	10.2
	No	No	6	75.0
		Bleeding	1	12.5
		Other	1	12.5
Treatment - Local Thrombolysis	Yes	No	10	41.7
		Bleeding	**6**	**25.0**
		Other	8	33.3
	No	No	92	89.3
		Bleeding	**6**	**5.8**
		Other	5	4.9

Part 2 – Long-Term Outcome

Out of 127 patients at baseline, 25 (19.7 %) were deceased at the time of long-term follow-up whereof eight patients (6.3 %) died in the acute phase. After exclusion of 37 patients (deceased n=25, living abroad n=4, onset age >63 years n=8), 90 patients were invited to the second part of the study including long-term follow-up. Ten patients declined participation, 28 could not be reached, ten did not decide whether they wanted to participate or not, one was excluded due to uncertain diagnosis and two because of severe underlying psychiatric illness. Altogether 39 patients participated in the long-term follow-up study, (clinical visit n=34, telephone n=5). Median length between diagnosis and follow up was 134 months (IQR 61 to 187). Four patients (10.5 %) had a recurrent thrombotic disease out of which two patients (5.3 %) had a recurrent CVT. Long-term outcome and residual symptoms are summarized in Table VII and VIII. According to the mRS about half of the patients (53.8 %) had no or mild symptoms and were able to resume pre-stroke activities (mRS 0 to 1). According to the BI all but three patients were independent in activities of daily living (94.7 %). The most self-reported complaints (Appendix I) at follow-up were memory or concentration disorder (n=24, 61.5 %), headache (n=15, 38.5 %), psychiatric problems (n=12,

31.6 %) and fatigue (n=11, 28.9 %). Seven patients (18.4 %) were free from symptoms at follow-up. Most patients had no or only mild neurological deficits (NIHSS score 0-2, n=31, 91.2 %). In Chi^2 tests, occurrence of fatigue, headaches, dizziness, speech disorder, motoric problems or psychiatric problems at follow-up, were all individually significantly associated with not having returned to work (p<0.044 for all).

Table VII. *Clinical outcome at long-term follow-up among patients surviving cerebral venous thrombosis (n=39).*

Modified Rankin Scale	**No. of cases**	**%**
0	8	21.1
1	13	34.2
2	11	28.9
3	5	12.8
4	1	2.6
5	0	0
Fully recovered (0-1)	21	55.3
Dependent (3-5)	6	15.4
NIHSS (5 missing)		
0-2	31	91.2
>2	3	8.8

NIHSS – National Institutes of Health Stroke Scale

Table VIII. Residual symptoms, and functional outcome at long-term follow-up among patients surviving cerebral venous thrombosis (n=39).

	No. of cases	**%**	**Missing data**		**No. of cases**	**%**	**Missing data**
Residual symptoms							
Epilepsy	4	10.3		Recurrent	4	10.5	1
Spasticity	0	0		Thrombosis			
Tremor	1	2.6	1	CVT	2	5.3	1
Headache	15	38.5		DVT	1	2.6	1
Memory or concentration disorder	24	61.5		LE	1	2.6	1
Dizziness	5	13.2	1	Barthel Index <100	3	5.3	1
Visual problem	6	15.8	1				
Linguistic disorder	9	23.7	1	Work return	28	71.8	
Pain	1	2.6	1	No work return	11	28.2	
Motor disorder	5	13.2					
Fatigue	11	28.9		Cryptogenic CVT	12	31.6	1
Psychiatric problems	12	31.6	1				
Other symptom	7	18.4	1				
No symptoms	7	18.4	1				

Vocational Outcome

Twenty-eight patients (71.8 %) were able to return to work within the follow-up period. Eleven patients (28.2 %) were still on sick leave or disability pension, all as a consequence of the residual symptoms from their CVT. Kaplan Meier plot is presented in Figure VI. The

cumulative proportion of patients who had returned to work at one, two, and three years where 48.7 %, 61.5 % and 71.8 %, respectively. Results from bivariate cox regression analyses are shown in Table IX. Time to work return was set as dependent factor. After adjusting for age and sex, absence of acute infarction, absence of acute intracranial event (subarachnoid hemorrhage, parenchymal hemorrhagic or non-hemorrhagic lesion, acute infarction), straight sinus thrombosis, estrogen use among women, and male sex were significantly associated with favorable outcome ($p<0.05$). Hematological condition, detected papilledema, multiple involvement of sinuses, mRS >2 upon discharge had p-values <0.1, but were not found significant after adjusting for age and sex. Based upon clinical- and theoretical experience, onset age >39, >2 risk factors, previous thrombosis and parenchymal or subarachnoid hemorrhage were put into a multivariable cox regression analysis, but no significance was found. The cohort was too small to perform further trustworthy multivariable analyses.

Table IX. *Predictors of work return after cerebral venous thrombosis.*

	Work return (n=28)	**No work return (n=11)**	HR	95 % CI	P	**Adjusted for age and sex** HR	95 % CI	P
Gender, male	12 (42.9)	3 (27.3)	1.859	0.86-4.04	0.117	**3.279**	**1.31-8.23**	**0.011**
Straight sinus thrombosis	7 (25)	0 (0)	2.430	1.01-5.87	0.049	**3.462**	**1.35-8.98**	**0.010**
Oral contraceptives*	8 (28.6)	2 (20)	3.027	1.11-8.29	0.031	**3.341**	**1.06-10.65**	**0.040**
Absence of acute infarction	23 (82.1)	4 (36.4)	3.004	1.13-8.00	0.028	**3.744**	**1.38-10.15**	**0.009**
Absence of acute intracranial event	13 (46.4)	2 (18.2)	2.867	1.33-6.19	0.007	**2.487**	**1.14-5.41**	**0.022**
Age <39	13 (46.4)	3 (27.3)	1.633	0.76-3.49	0.206	2.172	0.95-4.94	0.065
>1 sinus involved	27 (96.4)	6 (54.5)	8.404	1.14-62.14	0.037	7.616	0.98-58.99	0.052
Hematological condition (anemia, PV, ET)	1 (3.6)	0 (0)	6.923	0.8-59.3	0.077	3.826	0.43-34.26	0.230
Papilledema	5 (17.9)	0 (0)	2.979	1.06-8.35	0.038	1.875	0.58-6.07	0.294
mRS discharge >2	10 (35.7)	5 (45.5)	0.457	0.20-1.03	0.058	0.468	0.21-1.06	0.069

**Among women*
PV=Polycythemia Vera, ET=Essential Thrombocythemia, mRS=modified Rankin Scale
Numbers are presented as n (%)

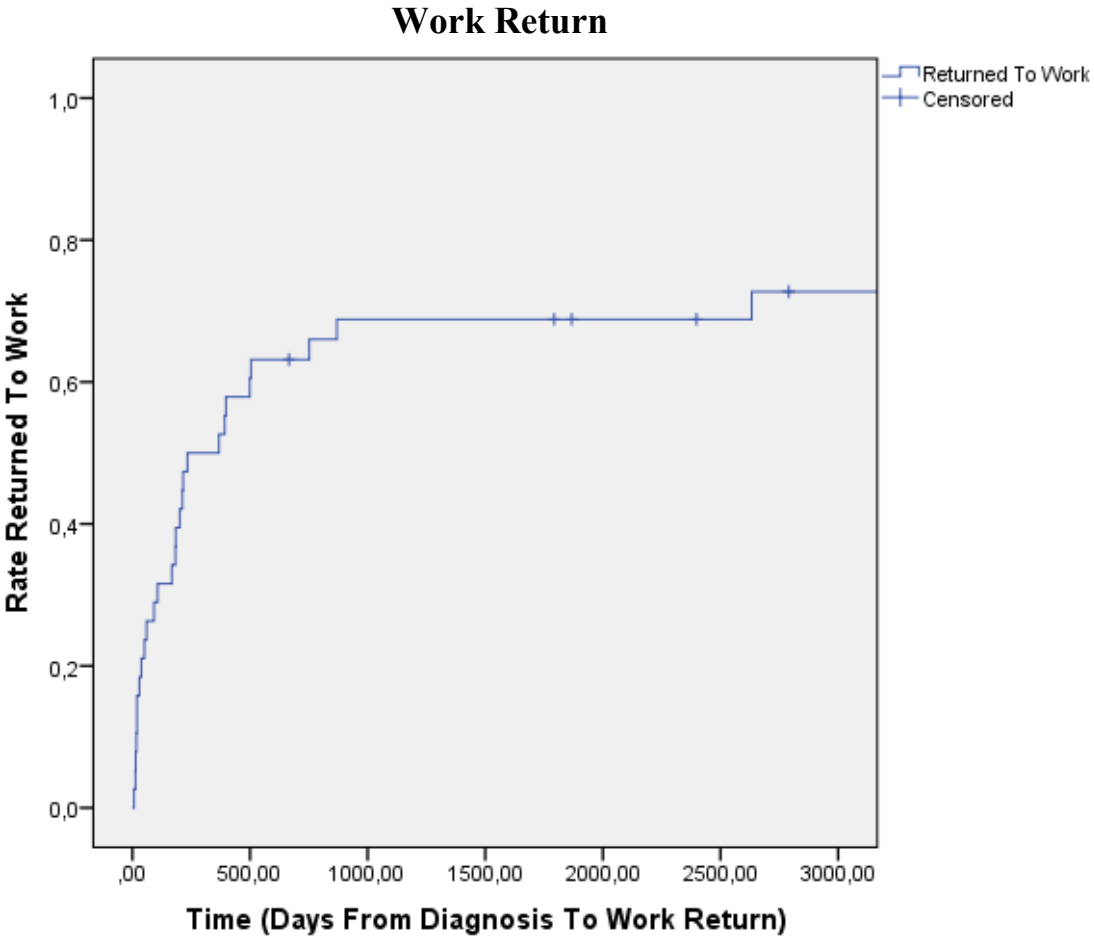

Figure VI. *Kaplan Meier plot on time to work return after diagnosis of cerebral venous thrombosis.*

Discussion

Description of Study and Main Findings

This single-center retrospective study including 127 consecutive CVT patients provides comprehensive data on clinical presentation, risk factors, radiological findings, and long-term functional outcomes. Our primary aim was to investigate long-term vocational outcome. Thirty-nine patients were evaluated at long-term follow-up. A vast majority of patients were functionally independent, scoring 0 to 2 on the mRS (n=32, 84.2 %). However, all but 18.4 % reported residual symptoms from CVT, and over one quarter (28.2 %) of the surviving patients were not able to return to work, following complications from their CVT. - Our

study suggests consequences of residual symptoms to negatively affect ability to return to work.

Demographics

The whole study population (n=127) differs from earlier studies with a somewhat older median age; 45 vs 37-39 years (8, 12). This may explain the relatively lower proportion of females (64.6 %, vs 74.5 % in ISCVT), who tend to be younger at onset as a result of gender-specific risk factors (8).

Clinical Presentation

Notably, almost all presenting symptoms were less frequent than in the ISCVT, despite the belief of elder patients being more severely affected, probably as a cause of the retrospective design (8). Nevertheless, the interrelationship between symptoms were very much alike previous studies. Contrary to the trend, 27.8 % presented with any seizure in comparison with 39.3 % in the ISCVT. Dichotomized to generalized seizures, the differentiation was less severe; 25.4% vs 30%, matching relatively less frequent parenchymal lesions on admission 52.8 % vs 62.9 % in the ISCVT and brain infarctions 40.9 % vs 46.5 % (8).

Inconsequent to more favorable presenting symptoms, our study population scored higher on the mRS at discharge compared to previous studies. Due to the retrospective design, a relative overestimation bias is possible. On the other hand, follow-up score assessed at clinical visit or by telephone, differed likewise. All assessments of mRS and NIHSS were performed by clinicians certified by a net-course from the University of Glasgow.

Risk Factors and Etiology

Found risk factors and etiology were very much in accordance with previous studies (8, 19, 51). Though, genetic thrombophilia was only found in 16.5 % of the cases, compared to 22.4 % in the ISCVT study (8). Although positive laboratorial findings ought to be documented in

medical records, some cases lacked data in the laboratorial module. Extensive laboratorial records were requested for, but not received at the end of the study. Again, retrospective designs have limitations compared to the ISCVT, where extensive laboratory investigations were encouraged. However, causes of thrombophilia were tested as a routine procedure throughout the study period. Interestingly, no patient had any known family history of CVT, but reliable data is lacking in most retrospective cases.

Gender-specific risk factors were frequently present in females, 51.9 % under age of 50 used oral contraceptive drugs comparable to 52 % in the ISCVT and 52.2 % in the Lille study (8, 51). Previous studies showed more favorable outcome in women with gender-specific risk factors, compared to other women and men (16).

Malignancy or intracranial tumor was found in 11 % of the patients (7.9 % malignancies). In the ISCVT 7.4 % cases were associated with cancer (8). Hence, the search for malignancy and tumors seems to be of utmost importance in CVT patients. An unpublished multicenter study, currently in progress in the Netherlands, will provide more statistical power on this matter by a larger number of patients, including the Gothenburg patient group (27). Etiology was not confirmed in as much as 31.6 % of the follow-up group, a substantial difference to the ISCVT cohort where only 12.5 % were cryptogenic (8).

Treatment, Complications, Radiological Findings

This study allowed inclusion of patients transferred to Sahlgrenska University Hospital, Gothenburg from other hospitals. Patients in need of neurointerventional techniques, usually in inferior condition, might have caused referral bias. In six patients (4.7 %) a dural arteriovenous fistula (DAF) was found. In the ISCVT population, merely 1.6 % presented

with fistulas (8). The relationship between CVT and DAF remains unknown. Future studies are needed to investigate what causes the other.

Local thrombolysis was performed to a greater extent (18.9 %) than in previous reports on other populations (ISCVT – 2.1 %). The matter is controversial, and there is a potential publication bias with under-reporting of cases with poor outcome and complications (7, 9). A randomized trial to evaluate local thrombolysis is currently ongoing (58). As presented in Table VI, patients receiving local thrombolysis were more likely to suffer from bleeding complications, 25 % vs 5.8 %. However, treated patients were probably already in severe clinical condition and at higher risk of fatal or irreversible consequences of the CVT. In the baseline group, almost all patients received treatment with subcutaneous or intravenous anticoagulation (n=118, 93.7 %). Bleeding occurred as a complication in 11 of these patients; however, 6 of them received simultaneous treatment with local thrombolysis.

Mortality in Hospital

Eight patients (6.3 %) died in the acute phase before leaving the hospital, slightly higher than in the ISCVT (4.3 %). At six months, no additional death had occurred, supporting previous rather low short-term mortality rates <10 % (14). Upon long-term follow-up, altogether 25 patients were deceased, but causes of death were not analyzed in this study. Previous studies have shown that patients surviving the acute phase are likely to die from underlying diseases rather than from complications to their CVT (47).

Long-Term Outcome

In a recently published international retrospective multicenter study (n=706), recurrence of CVT and VTE was 4.4 % and 6.5 % respectively (59), in accordance to our study, where 10.5 % had any recurrence of venous thrombosis and 5.3 % recurrence of CVT. In our study, few patients were spared from residual symptoms upon follow-up (18.4 %). Nevertheless, only

three patients scored <100 on the BI. Consistent with previous studies, occurrence of psychiatric problems (31.6 %), fatigue (28.9 %) and headache (38.5 %) were frequent (8, 53, 54). It must be noted that most residual symptoms were self-reported, although being evaluated and confirmed upon follow-up.

Vocational Outcome

All vocational analyses were performed based on self-reported employment data at risk for recall bias. However, at follow-up the self-reported employment data were discussed and evaluated. Additionally, patients were encouraged to validate specific dates of work return against any insurance document kept in their possession. According to the Kaplan Meier plot (Fig. VI), a shift where few patients return to work independent on further elapsed time occur approximately 800 days after diagnosis, indicating for CVT patients as group, most crucial recovery associated with work return have been achieved after 2 years. Working ability after CVT has only been investigated in small studies, largest so far conducted by Hiltunen et. al. ninety-one patients (75.2 % of 121 patients included in the vocational analysis) were employed at follow-up (53). In our study, 28 patients (71.8 %) were able to return to work within the follow-up period, and 11 (28.2 %) never regained their working ability. Even though having good outcome according to the mRS, more than a quarter were not able to return to work, suggestive of the mRS to be a rather imprecise tool when measuring long-term functional outcome in young adults. Non-medical aspects as national public economy, general employment rate, and sick retirement benefits and rules also affect employment rates. In comparison, sick leave rate overall in Sweden, last quarter of 2015, was 3.1 % (60). Unemployment in the Swedish population in general was 7.5 % (n=376700, 2015, ages 16-64, 7.7 % men n=201700, 7.3 % women n=175000). The more accurate number of unemployed according to the definition of this study would be even lower, due to the inclusion of full-time students in the unemployed group (women n=59 700, men n=61 700) (61).

Our study support previous reports on oral contraceptive use to be associated with more favorable outcome after CVT compared to other females (16, 53). Hiltunen et al. specifically reported a significant association between use of oral contraceptives at onset and being employed at long-term follow-up (OR 0.31, CI 0.10 to 0.95, p=0.040) (53). Further studies are needed to evaluate the mechanism.

Female sex has previously been reported associated with more favorable outcome compared to males (16). Contradictory, our analyses implies the male sex to have a better chance for returning to work, although the confidence interval is wide-ranging (HR=3.279, CI 1.31 to 8.23, p=0.011). Social gender aspects with different expectations on work return, both from the society and individually, may partly explain this difference.

Theoretically, straight sinus thrombosis is considered involved in more severe cases of CVT as a cause of a higher risk of diencephalon and mesencephalon damage. Contrary, our results suggest association with higher work return rate (HR 3.462, CI 1.35 to 8.98). Prior to the follow-up analyses, deceased cases were excluded and might have caused a selection bias. Therefore, the analysis was only taking survivors in concern. At baseline, straight sinus thrombosis was detected in 28 patients (22.2 %). Out of the eight patients deceased in the acute phase, six had straight sinus involvement. Merely seven of the remaining 22 were seen at long-term follow-up. Outcome following aggressive treatment could be either tremendously good, or tremendously bad. Additionally, extraordinary positive alteration in condition is possible to enhance the motivation to participate in a follow-up study, causing selection bias.

No development of infarction during acute hospital stay was significantly associated with work return after adjustment for age and sex, though the 95 % confidence interval was widely

spread (HR=3.774, CI 1.38 to 10.15). In the Helsinki study and a recent French study, no such association was detected (53, 62). Nevertheless, infarction in the acute phase predicting negative prognosis is both biologically plausible and supported in the ISCVT (8). Enlargement of the study group is likely to narrow the confidence interval.

Subgrouping of patients according to their clinical characteristics could be of benefit in clinical practice, due to the wide panorama of presentation and the rather heterogeneous CVT population. One subgrouping, easy to interpret and applicable in clinical practice is the occurrence of any intracranial event during the acute phase. Our study suggests absence of any intracranial event – parenchymal hemorrhagic/non-hemorrhagic lesion, infarction or subarachnoid hemorrhage, to have positive impact on work return (HR 2.487, 95 % CI 1.14 to 5.41).

Methodological Considerations

With a baseline population of 127 patients, this study contributes with one of the large single center CVT cohorts internationally. To our knowledge, this is the first Swedish study on cerebral venous thrombosis. An important strength of this study is the homogenous patient cohort, recruited from a predefined area which contributes to decrease risk of ascertainment bias.

The three most important limitations of the study are the partly retrospective design, the modest sample size, and the substantial loss of patients at follow-up. In cross sectional follow up studies, patients with events or active problems are more likely to respond. Also, self-reported symptoms are at risk for reporting bias, cognitive symptoms in particular. In future studies, objective assessment of cognitive problems would be of interest. Prospective studies, inevitably contribute more reliable data, however, retrospective studies contribute descriptive

data of great importance for creation of hypotheses, certainly in rare diseases where large patient materials are hard to reach.

All statistical results from part 2 of the study based on long-term follow-up data, must be evaluated taking the modest sample size into account. The uncertainty of results can be observed in the relatively wide ranged confidence intervals and the limited number of factors included in multivariable analyses. Enlargement of the patient cohort is likely to contribute to narrow the intervals, and increasing the statistical power.

This study provides interesting results, yet confirmations from studies with larger patient material are needed. The participation rate of less than 50 % of eligible patients is unsatisfactory, yet present. Recruitment of patients to this particular study is ongoing. A larger multivariable analyses could provide more reliable data on predictors of unemployment. Due to the relative rarity of CVT, such patient numbers can only be reached through international collaborations.

Conclusions

Although most CVT patients recovered well and were functionally independent, about a quarter of the survivors (28.2 %) were not able to return to work in the long-term. Individual predictors for work return were absence of acute intracranial event, absence of acute infarction, oral contraceptive use among females, straight sinus thrombosis, and male sex.

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Populärvetenskaplig Sammanfattning

Cerebral ventrombos (CVT): en studie med fokus på långtidsprognos och återgång till arbete

Erik Lindgren, 2016
Handledare: Turgut Tatlisumak och Katarina Jood

Cerebral ventrombos (sinustrombos) är ett relativt ovanligt tillstånd som innebär blodproppsbildning i hjärnans vensystem (blodkärl som för blodet tillbaka till hjärtat). I genomsnitt drabbas 8 personer per miljon invånare per år, främst unga i arbetsför ålder och företrädesvis kvinnor. De bakomliggande orsakerna är till viss del kända och utgörs av både ärftliga faktorer och miljöfaktorer, men för cirka en tredjedel av dem som drabbas kan man inte fastställa orsaken trots noggrann utredning. Vanliga riskfaktorer är p-piller, graviditet, vissa blodsjukdomar och cancer. Sinustrombos kan i akutskedet ge svår huvudvärk och även leda till hjärninfarkt och/eller hjärnblödning. Tillståndet kan få konsekvenser på längre sikt och det är inte ovanligt att drabbade rapporterar funktionsnedsättning som koncentrationssvårigheter, huvudvärk, uttröttbarhet, depression och epilepsi. Förhållandevis lite forskning har gjorts på sinustrombos med tanke på det stora värdet av god behandling och rehabilitering, inte bara för de unga individer som drabbas och deras anhöriga, utan även ur ett samhällsekonomiskt perspektiv.

Syftet med denna studie var därför att undersöka förekomsten av dessa följdsymptom mer noggrant och studera hur dessa symptom hör ihop med om patienter med sinustrombos kunnat återgå till arbete eller ej efter sin sjukdom.

Efter att ha granskat journaler från vuxna patienter som insjuknat eller behandlats för sinustrombos på Sahlgrenska Sjukhuset, Göteborg, mellan 1997 och 2015, kunde vi konstatera att de vanligaste symptomen vid insjuknande var huvudvärk, illamående och

kräkning. Tidigare forskning har presenterat liknande resultat. I studien undersöktes även patienter minst ett år efter sitt insjuknande för att studera kvarvarande symptom och om de kunnat återgå till arbete eller ej. Totalt deltog 39 patienter i denna uppföljning. Det visade sig att majoriteten mådde mycket bra rent fysiskt och var oberoende av hjälp för att klara av att utföra sina dagliga aktiviteter. Trots det, hade mer än en fjärdedel (28 %) av patienterna inte kunnat återgå till arbete efter sin sjukdom. Vissa faktorer och omständigheter var vanligare i gruppen som kunde gå tillbaka till arbete. Dessa faktorer var manligt kön, sinustrombos bland kvinnor som tagit p-piller, om man inte hade hjärninfarkt och om man inte hade förekomst av tecken på hjärnskador under röntgenundersökning.

Vår studie bekräftar alltså att trots att sinustrombos är en ovanlig sjukdom, så är den kritisk för de patienter som drabbas. Att vara ofrivilligt utesluten från arbetslivet har en negativ påverkan på livskvalitet, visar tidigare forskning. Det är svårt att samla stora grupper patienter från samma område, och internationella samarbeten behövs för att kunna göra mer tillförlitliga statistiska beräkningar. Ytterligare studier med fler patienter behövs för att bekräfta våra resultat för att vi i framtiden ska kunna identifiera och ge förbättrat stöd och behandling till de personer som har ökad risk att utveckla följdsymptom som påverkar återgång till arbete efter sinustrombos.

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Figures

Figure I (63)
Figure II (64)
Figure III (65)
Figure IV (64)

Appendices

Appendix I – Frågeformulär CVT långtidsuppföljning, del 2
Appendix II – Information till forskningsperson
Appendix III – Samtyckesblankett
Appendix IV – Frågeformulär till forskningsdeltagare
Appendix V – Frågeformulär CVT långtidsuppföljning, del 1