Prognosis of Cerebral Vein and Dural Sinus Thrombosis : Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)

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Prognosis of Cerebral Vein and Dural Sinus Thrombosis

Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)

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Background and Purpose—The natural history and long-term prognosis of cerebral vein and dural sinus thrombosis (CVT) have not been examined previously by adequately powered prospective studies.

Methods—We performed a multinational (21 countries), multicenter (89 centers), prospective observational study. Patients were followed up at 6 months and yearly thereafter. Primary outcome was death or dependence as assessed by modified Rankin Scale (mRS) score >2 at the end of follow-up.

Results—From May 1998 to May 2001, 624 adult patients with CVT were registered. At the end of follow-up (median 16 months), 356 patients (57.1%) had no symptom or signs (mRS=0), 137 (22%) had minor residual symptoms (mRS=1), and 47 (7.5%) had mild impairments (mRS=2). Eighteen (2.9%) were moderately impaired (mRS=3), 14 (2.2%) were severely handicapped (mRS=4 or 5), and 52 (8.3%) had died. Multivariate predictors of death or dependence were age >37 years (hazard ratio [HR]=2.0), male sex (HR=1.6), coma (HR=2.7), mental status disorder (HR=2.0), hemorrhage on admission CT scan (HR=1.9), thrombosis of the deep cerebral venous system (HR=2.9), central nervous system infection (HR=3.3), and cancer (HR=2.9). Fourteen patients (2.2%) had a recurrent sinus thrombosis, 27 (4.3%) had other thrombotic events, and 66 (10.6%) had seizures.

Conclusions—The prognosis of CVT is better than reported previously. A subgroup (13%) of clinically identifiable CVT patients is at increased risk of bad outcome. These high-risk patients may benefit from more aggressive therapeutic interventions, to be studied in randomized clinical trials. **(*Stroke*. 2004;35:664-670.)**

Key Words: cerebral veins ■ cranial sinuses ■ outcome ■ prognosis ■ thrombosis

Cerebral vein and sinus thrombosis (CVT) is rare compared with arterial stroke, and it often occurs in young people. Its clinical evolution seems to be different from other stroke subtypes and is highly variable between studies.[1] Reliable data on natural history and prognosis of CVT are scarce and are based mainly on single-center or single-country studies of modest size.[2–7] Treatment of sinus thrombosis with heparin is safe and is likely to improve its outcome.[8–10] Local endovascular thrombolysis may improve outcome in selected cases but has only been tried in small uncontrolled case series.[11] Despite improvements in diagnosis and treatment, dural sinus thrombosis may still cause death or permanent disability.[2–10]

The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) was initiated to obtain reliable evidence on clinical presentation, risk factors, outcome, and prognostic factors in a large prospective, multicenter series of patients with CVT.

Subjects and Methods

Organization of Study, Cases, and Case Ascertainment

ISCVT is a prospective multinational observational study that included consecutive patients (aged >15 years) with symptomatic CVT. All participants committed themselves to provide data on consecutive cases diagnosed at their institutions and to perform at least a 6-month follow-up observation. Case report forms with inclusion and follow-up data were sent to the coordinating center in Lisbon, Portugal. All data were cross-checked and validated at the end of the follow-up period. Inclusion started in May 1998 and continued until May 2001. Patients were followed up from diagnosis to December 31, 2002.

Most of the participants were neurologists. In order not to miss cases admitted to other departments, investigators were asked to disseminate information about the study in their hospitals and to search for cases in the emergency, imaging, intensive care, and other hospital departments.

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A complete list of the International Study on Cerebral Vein and Dural Sinus Thrombosis Investigators appears in Appendix 1.

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Imaging, Demographic and Clinical Data, Risk Factors, and Treatment

The diagnosis of CVT had to be confirmed by conventional angiography, CT venography, MRI combined with MR venography, surgery, or autopsy, following established diagnostic criteria.[1] Central review of the imaging results was optional.

We recorded the following information: demographic data; dates of onset of symptoms, of hospital admission, and of confirmation of the diagnosis by imaging (considered as day 0); symptoms and signs from onset to diagnosis; Glasgow Coma Scale (GCS) score on admission and during the clinical course; imaging methods used; location of the thrombus; and number, location, and size of any parenchymal lesions.

Presenting syndromes were dichotomized as isolated intracranial hypertension (any combination of headache, vomiting, and papill-edema with/without visual loss or sixth nerve paresis, without other neurological symptoms or signs) and other presenting syndromes.

A list of potential risk factors for CVT was attached to the inclusion form to assist investigators with the etiological workup (available at www.iscvt.com). Lumbar puncture (unless contraindicated) and thrombophilia screening (proteins C and S, antithrombin III, lupus anticoagulant, anticardiolipin antibodies, factor V Leiden, and G20210A mutations) were recommended.

The choice of treatment was left to the treating physician, but all treatments were systematically recorded.

Follow-up

Follow-up visits were performed at 6 months, at 12 months, and yearly thereafter, preferably by direct interview and observation by the local investigators. If that was not possible, alternative methods included telephone interview of the patient or interview of a relative or general practitioner. For patients who were lost to follow-up, the condition on the day of hospital discharge was regarded as the final follow-up. Follow-up data recorded were as follows: disability (according to modified Rankin Scale [mRS]),[12] death, recurrent symptomatic sinus thrombosis (new symptoms with new thrombus on repeated venogram or MRI), other thrombotic events, seizures, headaches requiring bed rest or hospital admission, severe visual loss (quantified with an optometric chart as $<4/10$), pregnancy, abortion, and current antithrombotic and other treatments.

Outcome

Outcome was classified according to the mRS as complete recovery (mRS 0 to 1); partial recovery, independent (mRS 2); dependent (mRS 3 to 5); and death (mRS 6). For patients who had a telephone follow-up, the mRS score was assessed by 3 previously validated questions.[13]

Primary outcome was death or dependence (mRS >2) at the end of the follow-up period. Secondary outcomes were death and death or dependence at 6 months. For patients who missed the 6-month evaluation but had the 1-year follow-up, we adopted the "worst Rankin" scenario: we used the mRS score either at discharge or at 1-year follow-up (whichever was worse) to estimate disability at 6 months.

Statistical Analysis

We considered demographic, clinical, and imaging variables and risk factors as possible explanatory variables of the outcomes (see Appendix 2, which is available online at http://stroke.ahajournals.org). Bivariate analysis was performed for each outcome with the χ^2 test (with Yates correction when necessary) or Fisher exact test for categorical data and with the Student t test or ANOVA for continuous data. Variables associated ($P<0.10$) with outcomes in the bivariate analysis were entered into a multivariate analysis.

For the outcome "death or dependence at the end of follow-up," we performed survival analysis using Kaplan-Meier and Cox regression statistics. We calculated the hazard ratios (HRs) and 95% CIs for the retained variables. For the remaining secondary outcomes, we performed a logistic regression analysis (backward method) and calculated odds ratios (ORs) and 95% CIs for the retained variables. Data were analyzed with SPSS 11.0 for Windows.

Results

Baseline Characteristics

Six hundred twenty-four adult cases were included in the study from 89 centers in 21 countries. The median delay from onset of symptoms to admission was 4 days (mean=14.5; SD=57.4 days) and from onset of symptoms to diagnosis 7 days (mean=18.3; SD=59.4 days). The diagnosis of CVT was established by MRI/MR venography in 443 patients (71%), by intra-arterial angiography in 74 (12%), by CT venography in 13 (2%), by multiple imaging methods in 89 (14%), and by surgery or autopsy in 5 (1%). The mode of onset was acute in 232 patients (37.2%), subacute in 346 (55.5%), and chronic in 45 (7.2%). One hundred forty-three patients (22.9%) presented with isolated intracranial hypertension. Eighty-three (13.9%) had a GCS score of between 9 and 13, and 31 (5.2%) were comatose (GCS <9). Demographic, clinical, and imaging features are shown in Table 1. Lumbar puncture was performed in 224 patients: opening pressure was >180 mm H_2O in 106 (83.5%), 71 had >5 cells (47.1%), and 96 (34.3%) had >45 mg/dL protein.

Investigation of thrombophilia was performed systematically in 75% of the centers. Risk factors are summarized in Table 2. Thrombophilia, either genetic or acquired, and oral contraceptives were the most common risk factors. Many patients (272 [43.6%]) had >1 known risk factor.

In the acute phase, most patients (520 [83.3%]) were anticoagulated with intravenous heparin (401 cases [64%]) or subcutaneous low-molecular-weight heparin (LMWH) (218 patients [34.9%]) in therapeutic dosages. A few patients received only subcutaneous LMWH in prophylactic dosage (9 patients [1.4%]) or antiplatelet drugs (37 patients [5.9%]). Thirteen patients (2.1%) were treated with local endovascular thrombolysis. Additional treatments included antiepileptic drugs (277 patients [44.4%]), osmotherapy (82 [13.2%]), steroids (150 [24.1%]), acetazolamide (61 [9.8%]), and diuretics (34 [5.5%]). Shunts were performed in 10 patients (1.6%), 9 (1.4%) had decompressive craniotomy or hematoma evacuation, and 7 (1.1%) required mechanical ventilation.

Outcome

Information on outcome at discharge was available for all patients (Table 3). Median hospital stay was 17 days (mean=20.4, SD=14.3). Thirty-day case fatality was 3.4% (21 cases).

Six-month follow-up was assessed by face-to-face interview in 432 patients (77%), by telephone interview in 91 (16.3%), by other means in 27 (4.8%), and not specified in 10 (1.8%). Thirty-seven patients (6%) missed the 6-month evaluation but had subsequent follow-ups. At 6 months, 437 patients (79.6%) were on oral anticoagulation.

At the end of the study we had follow-up information for 98.7% of the patients. Eight patients (1.3%) were lost to follow-up after discharge. The last follow-up was performed by face-to-face interview in 358 patients (61%), by telephone

TABLE 1. Demographic, Clinical, and Imaging Features of Included Patients

	No. of Cases	Missing Data	%
Mean age=39.1 y (range 16–86)			
Median age=37 y			
Female	465		74.5
Ethnicity		3	
White	492		79.2
Black	31		5
Asian	21		3.4
Hispanic	58		9.3
Other	19		3.1
Symptoms and signs			
Headache	553	1	88.8
Visual loss	82	3	13.2
Papilledema	174	10	28.3
Diplopia	84		13.5
Stupor or coma	87		13.9
Aphasia	119		19.1
Mental status disorders	137		22
Left paresis	127		20.4
Right paresis	127		20.4
Any paresis	232		37.2
Bilateral motor signs	22		3.5
Focal seizure	122		19.6
Seizure with generalization	187		30
Any seizure	245		39.3
Sensory symptoms	34		5.4
Other focal cortical sign	21		3.4
CT/MRI infarct	290	1	46.5
Left hemisphere	193		31
Right hemisphere	172		27.6
Posterior fossa	20		3.2
CT/MRI hemorrhage	245	2	39.3
Left hemisphere	154		24.8
Right hemisphere	113		18.2
Posterior fossa	10		1.6
Any parenchymal lesion on CT/MRI	392		62.9
Bilateral parenchymal lesions on CT/MRI	112		18
Posterior fossa parenchymal lesions on CT/MRI	26		4.2
Occluded sinus/vein			
Superior sagittal sinus	313		62.0
Lateral sinus, left	279		44.7
Lateral sinus, right	257		41.2
Straight sinus	112	1	18.0
Deep venous system	68	2	10.9
Cortical veins	107	1	17.1
Jugular veins	74		11.9
Cerebellar veins	3	2	0.3
Cavernous sinus	8	1	1.3

TABLE 2. Risk Factors Identified in Included Patients

	No. of cases	%
None identified	78	12.5
Thrombophilia	213	34.1
Genetic	140	22.4
Acquired	98	15.7
Antiphospholipid antibody	40	5.9
Nephrotic syndrome	4	0.6
Hyperhomocysteinemia	28	4.5
Malignancy	46	7.4
CNS	14	2.2
Solid tumor outside CNS	20	3.2
Hematological	18	2.9
CNS disorders	12	1.9
Dural fistulae	10	1.6
Venous anomaly	1	0.2
Arteriovenous malformation	1	0.2
Hematological condition	75	12
Polycythemia, thrombocythemia	18	2.8
Anemia	58	9.2
Vasculitis	19	3
Systemic lupus erythematosus	7	1
Behçet disease	6	1
Rheumatoid arthritis	1	0.2
Thromboangiitis obliterans	1	0.2
Nonspecified	4	0.6
Other inflammatory systemic disorders	11	1.8
Intestinal inflammatory disease	10	1.6
Sarcoidosis	1	0.2
Other systemic disorders	15	2.4
Thyroid disease	11	1.7
Other	4	0.6
Pregnancy*	24	6.3
Puerperium*	53	13.8
Infection	77	12.3
Central nervous system	13	2.1
Ear, sinus, mouth, face, and neck	51	8.2
Other	27	4.3
Mechanical precipitants	28	4.5
Lumbar puncture	12	1.9
Cranial trauma	7	1.1
Jugular catheter occlusion	5	0.8
Neurosurgery	4	0.6
Drugs	47	7.5
Oral contraceptives*	207	54.3
Hormone replacement therapy	27	4.3
Steroid	10	1.6
Cytotoxic	5	0.8
Other	5	0.8
Surgery	17	2.7
Dehydration	12	1.9

Cases may have >1 risk factor. *Percentages among 381 females <50 years of age.

TABLE 3. Outcome at Discharge, 6 Months, and Last Follow-Up

	Outcome at Discharge (n=624)		Outcome at 6 Months (n=616)		Outcome at Last Follow-Up (n=624)	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Modified Rankin Scale						
0	170	27.2	284	46.1	356	57.1
1	240	38.5	197	32	137	22
2	96	15.4	49	8	47	7.5
3	43	6.9	24	3.9	18	2.9
4	33	5.3	16	2.6	10	1.6
5	15	2.4	4	0.6	4	0.6
Death	27	4.3	42	6.8	52	8.3
Complete recovery	410	65.7	481	78.1	493	79
Death or dependency	118	18.9	86	14.0	84	13.4

in 189 (32%), by other means in 29 (4.9%), and not specified in 13 (2%). Median length of follow-up was 16 months (mean=18.6, SD=11.1). Median time on oral anticoagulants after discharge was 231 days (7.7 months). Eleven of the 25 deaths (44%) that occurred after the acute phase were not caused by sinus thrombosis but by an underlying condition. There were no significant differences in outcome between patients enrolled in different countries or world regions. Patients presenting with isolated intracranial hypertension syndrome had a better outcome (10 dead/dependent [7%]) than the remaining patients (75 dead/dependent [13.6%]; HR=0.45; 95% CI, 0.23 to 0.87). We found a nonsignificant difference in outcome in favor of the patients who were anticoagulated in therapeutic doses in the acute phase (66/520 [12.7%] dead/dependent versus 19/104 [18.3%]; HR=0.73; 95% CI, 0.44 to 1.21). Results of the Cox regression analysis at last follow-up are shown in Table 4.

Results of logistic regression analysis for secondary outcomes are shown in Table I, which is available online at http://stroke.ahajournals.org.

Events occurring during follow-up are shown in Table 5. Thirty-four women became pregnant after CVT. There were 9 abortions (4 spontaneous, 5 voluntary) and 21 (61.7%) uneventful pregnancies. Complications in the remaining 4 pregnancies included recurrent CVT (1 patient) and limb or pelvic venous thrombosis (2 patients) and seizures (1 patient). Only 1 woman who suffered recurrent thrombotic events was on LMWH. Among the 77 women who had CVT related to pregnancy or puerperium, 8 had uncomplicated new pregnancies, 1 pregnant woman experienced a seizure, and there were 1 spontaneous and 2 voluntary abortions.

TABLE 4. Outcome at Last Follow-Up (Cox Regression Analysis)

	Death or Dependency			
Predictor	n/N	%	Hazard Ratio	95% CI
Age >37	26/312	8.3	2.00	1.23–3.27
Male sex	32/159	20.1	1.59	1.01–2.52
Mental status disorder	37/137	27.0	1.95	1.23–3.09
GCS <9	12/31	38.7	2.65	1.41–4.55
Deep venous system thrombosis	20/68	29.4	2.92	1.70–5.00
Intracranial hemorrhage	47/245	19.2	1.88	1.17–3.03
Any malignancy	15/46	32.6	2.90	1.60–5.08
CNS infection	4/13	30.8	3.34	1.98–17.24

n=number of patients with the outcome and predictor; N=total patients with predictor.

Discussion

The main objectives of this prospective multicenter international study were achieved. This is the largest cohort ever published (624 CVT patients) collected over a short period of time, with the largest follow-up (median 16 months). The prognosis was better than reported previously. Nevertheless, 8% died, either as a direct consequence of CVT or due to an underlying condition. Risk factors for an unfavorable outcome were identified and included male sex, age >37 years, coma, mental status disorder, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system (CNS) infection, and cancer.

Strengths of the study include the collaboration between many types of hospitals in different countries and continents,

TABLE 5. Events During Follow-Up

	No. of Cases	%	95% CI
Recurrent sinus thrombosis*	14	2.2	1.3–3.7
Other thrombotic events*	27	4.3	3.0–6.2
Limb or pelvic venous thrombosis	16	2.5	1.6–4.1
Pulmonary embolism	3	0.5	0.2–1.4
Stroke	2	0.3	0.1–1.2
TIA	2	0.3	0.1–1.2
Acute limb ischemia	4	0.7	0.2–1.6
Seizures	66	10.6	8.4–13.2
Severe headache	88	14.1	11.6–17.1
Severe visual loss	4	0.6	0.2–1.6

*Seventeen (41.5%) patients were on anticoagulants at the time of the event.

TABLE 6. Death or Dependency at the End of the Follow-Up: Data From Prospective Studies With Long-Term Follow-Up

Study	Follow-Up Mean Time, mo	Death/ Dependency Yes/No	%	95% CI	Weight %
Rondepierre	6	8/10	44.4	24.6–66.3	1.9
Preter	78	18/67	21.2	13.8–31.0	9.1
De Bruijn	19	11/44	20	11.6–32.4	5.9
VENOPORT	22	8/83	8.8	4.5–16.4	9.7
Breteau	36	10/45	18.2	10.2–30.3	5.9
Cakmak	3	2/14	12.5	3.5–36.0	1.7
ISCVT	18	84/532	13.6	11.2–16.6	65.8
Total		141/795	15.1	12.9–17.5	100.0

Test for heterogeneity $\chi^2=30.04$; df=6; $P<0.00001$.

which diminishes potential inclusion bias. CVT was confirmed in all cases with current technology and established consensus criteria. Completeness of follow-up was satisfactory, with only 1.3% lost after discharge. Methodological limitations of the study include lack of central review of imaging and absence of uniform etiological workup or treatment. Nevertheless, an extensive search for risk factors was pursued in the majority of the patients, as supported by the small number (12.5%) of patients without identified risk factors. Notably, a systematic search for thrombophilia was performed in 75% of the centers. More than 80% of the patients were anticoagulated with therapeutic doses of heparin.

Incomplete case ascertainment is a possible source of bias. Since the majority of the participants are neurologists, we may have missed severe cases admitted to intensive care units and therefore underestimated death and disability. To decrease this potential bias, investigators were asked repeatedly to search for cases through imaging and other hospital departments and intensive care units.

Because the ISCVT has a pragmatic design and included patients from 89 centers in 21 countries, results of this study are generalizable to CVT patients around the world with the exception of Africa or Asia because very few patients from these continents were included. A higher frequency of CVT related to infections, anemia, and pregnancy/puerperium[14,15] and a less favorable outcome for CVT patients in these continents are possibilities that need to be verified. ISCVT results do not apply to children, who may have a worse prognosis than adults.[16]

Before ISCVT, only 6 prospective studies examined the long-term outcome after CVT.[2–7] These studies were based on a single center or single country and had modest sample sizes. These features limit their statistical power and generalizability. Results from these series concerning death and disability were contradictory (Table 6), perhaps related to referral bias. Total death rate at the end of follow-up in the aforementioned studies ranged from 0%[7] to 39%.[2] The death/dependence rate at the end of follow-up varied from 9%[5] to 44%,[2] while in ISCVT only 13% of the patients either had died or were dependent at the end of follow-up.

Deaths during follow-up were as frequent as acute deaths but were predominantly related to underlying diseases, such as malignancies. Very few patients remained dependent. This finding contrasts with the outcome from arterial stroke types, in which the proportion of permanently dependent patients ranges between one third and two thirds of the survivors.[17]

Long-term prognostic factors were analyzed by multivariate methods in 3 previous studies.[4–6] ISCVT confirmed coma,[4] cerebral hemorrhage,[4] and malignancy[6] as important prognostic factors for death or dependence. In addition, we identified male sex, age >37 years, mental status disorder, thrombosis of the deep cerebral venous system, and CNS infection as variables that increase the risk of death or dependence. Seizures (10%) and new thrombotic events (4%) were the most frequent complications during follow-up. Recurrence of CVT and severe visual loss were exceptional but severe and potentially preventable occurrences. Except for spontaneous abortions, other complications rarely occurred during or after new pregnancies. These findings strongly support the evidence that past CVT (including puerperal CVT) is not a contraindication to pregnancy.[18,19]

Our results have implications for clinical practice concerning the investigation, treatment, and prognosis of patients with CVT. We found that patients with CVT usually have multiple risk factors. Therefore, the identification of 1 risk factor (eg, contraceptives, infection) should not stop the search for additional risk factors, in particular inherited or acquired thrombophilia. More than 80% of the patients were treated with anticoagulants, indicating a consensus among most participants on the efficacy and safety of anticoagulation in the acute phase of CVT.[10] The ISCVT has identified easily available variables that predict an unfavorable outcome. Patients with these characteristics deserve additional close monitoring, and some may be candidates for more aggressive interventions, such as local thrombolysis and reduction of intracranial pressure.

The results of our study also have implications for research. Future randomized clinical trials of aggressive and potentially hazardous interventions such as local thrombolysis[11] or decompressive craniectomy[20] should be targeted at high-risk patients. Because of the comparative rarity of CVT, such studies can only succeed through international collaborative efforts such as that initiated in the ISCVT.

Appendix 1

ISCVT Group

Steering Committee

J.M. Ferro, J. Stam, M-G. Bousser, F. Barinagarrementeria, K. Einhäupl.

Coordinating Office

J.M. Ferro, P. Canhão, Marisa Costa.

Participants

The following centers and investigators participated in the ISCVT. The number of patients included at each center is given in parentheses. Hôpital Lariboisière Paris, France (49, M-G. Bousser and I. Crassard); Instituto Nacional de Neurologia y Neurocirurgia, Mexico

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