

Causes and Predictors of Death in Cerebral Venous Thrombosis

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Background and Purpose—The causes of death of patients with cerebral venous thrombosis (CVT) have not been systematically addressed in previous studies. We aimed to analyze the causes and predictors of death during the acute phase of CVT in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) to identify preventable or treatable causes.

Methods—ISCVT is a multinational, prospective, observational study including 624 patients with CVT occurring between May 1998 and May 2001, in which 27 patients (4.3%) died during the acute phase, 21 (3.4%) within 30 days from symptom onset. Inclusion forms and a questionnaire assessing the causes of death were analyzed. A logistic regression analysis was performed to identify the predictors of death within 30 days from symptom onset of CVT.

Results—Median time between onset of symptoms and death was 13 days and between diagnosis and death, 5 days. Causes of death were mainly transtentorial herniation due to a unilateral focal mass effect (10 patients) or to diffuse edema and multiple parenchymal lesions (10 patients). Independent predictors of death were coma (odds ratio [OR], 8.8; 95% confidence interval [CI], 2.8 to 27.7), mental disturbance (OR, 2.5; 95% CI 0.9 to 7.3), deep CVT thrombosis (OR, 8.5; 95% CI, 2.6 to 27.8), right intracerebral hemorrhage (OR, 3.4; 95% CI, 1.1 to 10.6), and posterior fossa lesion (OR, 6.5; 95% CI, 1.3 to 31.7). Worsening of previous focal or de novo focal deficits increased the risk of death.

Conclusions—The main causes of acute death were neurologic, the most frequent mechanism being transtentorial herniation. (*Stroke*. 2005;36:1720-1725.)

Key Words: cerebral veins ■ cerebrovascular circulation ■ death ■ models, statistical
■ prognosis ■ sinus thrombosis

Cerebral vein and dural sinus thrombosis (CVT) is an infrequent stroke type often described as having an unpredictable outcome.¹ In the past, CVT was diagnosed almost exclusively at autopsy and thought to be almost always fatal.²⁻⁴ In early angiographic series, mortality ranged between 30% and 50%.⁵ In recent series, widely discrepant proportions of case fatality ranging from 4% to 33% were reported.⁶⁻¹¹ In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), 4.3% of patients died during the acute phase of CVT and 3.4% within 30 days from symptom onset.¹² In the ISCVT, a small percentage of patients remained dependent, and acute death was a determinant in the outcome “death or dependency” at the end of the follow-up, making it worthwhile to perform a separate analysis of acute death. Furthermore, the cause of death was seldom evaluated, especially in larger samples of patients. If causes of death could be identified, specific treatments could

be planned to prevent fatality. The objectives of the present study were to (1) analyze case fatality during the course of CVT in the ISCVT; (2) describe the main causes of death; and (3) identify predictors of death.

Methods

Study Population

This study comprised patients with proven CVT who were included in the ISCVT, described in detail elsewhere.¹² Briefly, the ISCVT is a prospective, multinational observational study that included 624 consecutive patients (age >15 years) with symptomatic CVT occurring between May 1998 and May 2001. The diagnosis of CVT was confirmed by conventional angiography, computed tomography venography, magnetic resonance imaging (MRI) combined with MR venography, or at surgery or autopsy, according to established diagnostic criteria.¹

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Data Collection

The following data were obtained in the ISCVT study: demographics; dates of symptom onset; hospital admission and diagnosis; symptoms and signs from onset to diagnosis; Glasgow Coma Scale (GCS) score on admission; location of the thrombus; number, size, and location of parenchymal lesions; risk factors; type of worsening (decreased consciousness, new focal deficits, worsening of previous focal deficit, seizures, other); treatment; and outcome. Presenting syndromes were dichotomized as isolated intracranial hypertension (any combination of headache, vomiting, and papilledema with or without visual loss or VI nerve paresis, without other neurologic symptoms or signs), and other presenting syndromes.

In addition, a questionnaire was sent to the investigators for each patient who was reported to have died during the course of CVT. The causes of death were classified as (1) cerebral transtentorial herniation secondary to diffuse edema or multiple bilateral lesions (hematoma or infarct) or to a unilateral focal mass effect (hematoma or infarct)¹³; (2) pulmonary embolism¹⁴; (3) neurogenic pulmonary edema¹⁵; (4) generalized status epilepticus; (5) underlying disease; (6) sudden (<1 hour) unwitnessed death; (7) any combination of the above; or (8) other.

Outcome

All patients who died during hospitalization for the inclusion episode of CVT were analyzed, and their causes of death were assessed. Deaths occurring during follow-up were not the subject of the present analysis. We compared the causes of early death (before the median time between the onset of symptoms and death) with those of late death (after the median between the onset of symptoms and death).

For analysis of the predictors of death, the outcome of interest was mortality within 30 days of onset of CVT symptoms. Because the duration of hospitalization was variable, we analyzed follow-up data to identify patients who died after discharge but within 30 days after onset of symptoms.

Statistical Analysis

Descriptive statistics were performed to describe the CVT patients who died. For continuous variables, means, standard deviations, medians, and ranges were calculated. For categorical variables, numbers and percentages for each category were tabulated.

Comparisons were made between CVT patients who died and survivors. Bivariate analysis was performed for the outcome "death within 30 days" with the χ^2 (with Yates' correction when necessary) or Fisher exact test for categorical data and with Student's *t* test for continuous data. We performed a logistic regression analysis (backward method) and calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the retained variables associated with the outcome "death" in the bivariate analyses ($P < 0.10$). The specificity and sensitivity of the model for prediction of death were calculated. Data were analyzed with SPSS 11.0 for Windows.

Results

Description of Patients

Six hundred twenty-four adult patients were included in the ISCVT from 89 centers in 21 countries. Twenty-seven patients (4.3%) died during the inclusion episode of CVT, 21 (3.4%) within 30 days after symptom onset. None of these deaths occurred after discharge.

Death occurred a median of 13 days (mean, 21.2 days; SD, 24.5) after symptom onset, a median of 5 days (mean, 11.3 days; SD, 15.8) after diagnosis. Concerning patients who died within 30 days from symptom onset, death occurred a median of 9 days (mean, 10.6 days; SD, 6.4) after symptom onset and a median of 4 days (mean, 5.3 days; SD, 4.5) after diagnosis. Table 1 describes baseline characteristics and risk factors for CVT in patients who died during the course of CVT.

No difference was found in the time from onset of symptoms to admission or to the diagnosis of CVT in patients who died compared with those who survived. Mental status disorders ($P < 0.001$), impaired consciousness ($P < 0.001$), and seizures ($P = 0.002$) at admission were more frequent in patients who died, whereas isolated intracranial hypertension syndrome was less frequent ($P = 0.023$). Thrombosis of the superior sagittal sinus ($P = 0.023$), cortical veins ($P = 0.004$), deep cerebral veins ($P < 0.001$), parenchymal lesions ($P = 0.002$), hemorrhagic lesions ($P = 0.002$), right hemorrhagic lesions ($P = 0.001$), and posterior fossa lesion ($P = 0.004$) were more frequent at admission in patients who died. Size of parenchymal lesions was significantly higher in patients who died during the acute phase. Twelve of 25 (48%) had parenchymal lesions > 5 cm in their larger diameter, in contrast to 106 of 558 surviving patients (19%; OR, 3.9; 95% CI, 1.8 to 8.9; $P < 0.001$).

All patients who died deteriorated during the course of the inclusion episode (median of 2 days after admission; mean, 6.2; SD, 10.6; Table 2). Among patients who died within 30 days from symptom onset, the following types of worsening were more frequent: altered mental state ($P < 0.001$), worsening of previous focal deficit ($P < 0.001$), and new focal deficit ($P < 0.001$). New lesions on subsequent neuroimaging examinations were more frequent among those who died ($P < 0.001$), either infarct or edema ($P = 0.007$), or hemorrhage ($P < 0.001$).

All but 2 of the 27 patients who died were treated with heparin (Table 2), a similar proportion compared with those who survived. Thrombolytic therapy was administered in 5 patients who deteriorated despite other treatments, locally in the thrombus in 4 patients, and systemically in 1 patient.

Causes of Death

The investigators returned 21 of 27 questionnaires. Two independent investigators adjudicated the cause of death by using the questionnaires and the inclusion form data (Table 2). The most frequent cause of death was transtentorial herniation, due to either a focal mass effect (10 patients) or to multiple lesions and edema (10 patients).

Causes of Early and Late Death

The causes of early death (13 patients) were different from those of late death (14 patients). Early deaths were due to transtentorial herniation because of multiple lesions, diffuse edema (7 patients), and a focal mass effect (6 patients). Late deaths were less frequently due to transtentorial herniation (7 patients); cardiopulmonary arrest in a patient with leukemia; sudden death in a patient with multiple cerebral hemorrhages and respiratory distress; underlying disease in an HIV-infected patient; pulmonary embolism and intracranial hypertension due to diffuse edema in 1 patient who was treated with heparin; sepsis in 2 patients; and unclassified in 1 patient.

Predictive Models of Death

A logistic multivariate analysis identified the following independent variables predicting death within 30 days from symptom onset: seizure, mental status disorder, GCS score

TABLE 1. Baseline Characteristics, Imaging, and Risk Factors of Patients Who Died During Hospitalization for CVT

Patient No.	Age, y	Sex	Onset	Symptoms/Signs Until Admission	GCS	CT/MRI Lesion	Thrombosis	Risk Factors for CVT
1	35	M	Acute	Mental, L paresis, focal seizure, hemianopsia	14	R hem and inf	SSS	ALL, LP, l-asparaginase
2	33	M	Chronic	Headache, papilledema, diplopia, mental	15	R hem	SSS, SS	
3	25	F	Subacute	Headache, aphasia, mental, coma	MD	L hem and inf	SSS, R and L LS	
4	46	F	Subacute	General seizure	15	L hem, SAH	R LS	
5	75	M	Subacute	Headache, papilledema, vertigo	15	No	L LS, L jugular	Leukemia
6	53	M	Subacute	Headache, L paresis, general seizure	15	R hem	SSS, CV	Protein C deficiency
7	29	F	Acute	Headache, coma	6	No	SSS, L and R LS, SS, CV, DVS	OC
8	39	M	Acute	Headache, papilledema, aphasia, mental, R paresis	12	R and L hem	SSS, L LS, SS, L jugular	Dehydration, polycythemia
9	30	F	Subacute	Headache, papilledema, mental, coma	5	L and post fossa inf	SSS, SS, DVS	Puerperium
10	74	F	Subacute	Aphasia, mental, coma, general seizure	6	R and L hem and inf	SSS, L and R LS, CV	Dehydration, head trauma
11	48	F	Subacute	Headache, mental, coma	5	R and L inf	DVS	Anemia, APCr, arthritis, danazol, salazopyrine
12	23	F	Subacute	Headache, focal and general seizures, coma	MD	R and post fossa inf	SSS, L and R LS, SS	
13	40	F	Acute	Headache, general seizure, sensory L	6	R and L hem	SSS, R LS, DVS, jugular	OC
14	47	F	Acute	Headache, diplopia, mental, aphasia, L paresis, seizure, coma	3	R hem and inf	SSS, L LS, DVS	OC, anemia
15	42	F	Acute	Headache, mental, coma	9	L hem and inf	SS, DVS	MEA disorder
16	36	M	Subacute	Headache, papilledema, aphasia, general seizure, coma	13	L hem	SSS, L and R LS, R jugular	
17	27	F	Subacute	Headache, diplopia, R paresis, focal seizure	15	L inf and post hem	SSS, L and R LS, SS, DVS	OC, ENT, leg thrombosis
18	65	M	Acute	Coma, bilateral paresis, general seizure	7	R hem, bilat inf	SSS, CV	HIV, ENT, lumbar puncture
19	25	F	Subacute	Headache, mental, aphasia, L paresis, coma	11	R hem, bilat inf	SSS, L and R LS, SS, CV, DVS	OC
20	28	F	Acute	Headache, mental, L paresis, general seizure	14	R hem	SSS, CV	Puerperium
21	25	M	Acute	Headache, papilledema, mental, paresis, general seizure	11	R hem	SSS, CV	
22	37	F	Acute	Headache, papilledema, bilateral paresis, general seizure	12	R hem	SSS, CV	Puerperium, anemia
23	22	F	Acute	Headache, papilledema, coma, R paresis, general seizure	6	R, L, and post inf	SSS	Meningitis, ENT, endocarditis
24	81	M	Subacute	Headache, mental, coma, general seizure	3	R hem, bilat inf	SSS, L and R LS, CV	ENT, septic shock
25	31	F	Subacute	Headache, papilledema, mental, L paresis, focal and general seizures	14	R and L inf	SSS, L and R LS, SS, CV, DVS	OC
26	49	F	Subacute	Headache, L paresis	15	R hem and inf	SSS, R LS	Prothrombin mutation
27	69	M	Subacute	Headache, visual loss, aphasia, focal seizure	15	L hem and inf	SSS, CV	

Mental, MD indicates mental disorder; L, left; R, right; Hem, hemorrhagic; inf, infarct; SAH, subarachnoid hemorrhage; post, posterior; bilat, bilateral; SSS, superior sagittal sinus; SS, straight sinus; LS, lateral sinus; CV, cortical vein; DVS, deep cerebral venous system thrombosis; ALL, acute lymphocytic leukemia; LP, lumbar puncture; OC, oral contraceptive; APCr, activated protein C resistance; MEA, multiple endocrinopathy adenomatosis; ENT, ear-nose-throat infection; and MD, missing data.

<9 at admission, deep CVT, and right hemorrhage and posterior fossa lesions on the initial MRI or computed tomography scan (Table 3).

We added to the previous predictive model the variables corresponding to the different types of worsening except "worsening of consciousness" to avoid including the out-

TABLE 2. Treatments, Clinical Course, and Causes of Death in Patients With CVT

Patient No.	Antithrombotic Treatment	Other Treatments	Type of Worsening	New Lesions	Cause of Death
1	Heparin, local urokinase	ACV, steroids, antiosmotics	Mental, coma	Yes	Herniation (hem)
2	LMWH	Steroids	Sudden death	NK	Herniation (hem)
3	LMWH		Prev and new focal, consc	Yes	Herniation (hem)
4	Heparin	ACV, steroids, antiosmotics	Consc	Yes	Herniation (hem)
5	Heparin	ACV, steroids	New focal, consc, seizure, mental	No	Cardiac/respiratory arrest
6	Heparin, local fibrinolysis	ACV	New focal, consc, seizure, mental	Yes	Herniation (hem)
7	LMWH, heparin, IV fibrinolysis	ACV	Mental, consc	Yes	Herniation (M hem and edema)
8	LMWH	ACV, steroids, antiosmotics, ventilation	Prev and new focal, consc, seizure; medical	Yes	Sepsis, M hem, and edema
9	Heparin		Consc	NK	Herniation (M inf and edema)
10	Heparin	ACV		NK	
11	Heparin		Consc	Yes	Herniation (M hem)
12	Heparin			NK	Herniation (M inf and edema)
13	LMWH, local urokinase	ACV, sedation	Prev and new focal, consc, mental	Yes	Herniation (M hem and edema)
14	Heparin	ACV	Prev focal, consc, seizure	Yes	Herniation (M hem and edema)
15	Heparin	ACV, steroids, antiosmotics	Prev focal, mental, consc	Yes	
16	Heparin	ACV, steroids, antiosmotics	New focal, consc	No	Herniation (hem)
17	heparin	ACV, antibiotics, shunt	Prev and new focal, consc, mental	Yes	Herniation (hem)
18	LMWH	ACV, antiosmotics	Prev focal, consc, seizure	No	Underlying disease (HIV)
19	Heparin; fibrinolysis, and thrombosuction	ACV, antiosmotics, ventriculostomy	Prev and new focal, consc, mental	Yes	Herniation (M hem and edema)
20	Heparin	ACV, antiosmotics	Prev focal, consc	No	Herniation (hem)
21	Heparin	ACV, antiosmotics	Prev and new focal, consc	Yes	Herniation (M hem and edema)
22	Heparin	ACV, antiosmotics	Consc	NK	Herniation (hem)
23		ACV	Consc	Yes	Sepsis, NPE (M hem and inf)
24	Heparin	ACV, steroids	Consc, new focal	Yes	PE, intracranial hypertension, edema
25	Heparin	ACV, steroids, antiosmotics	Prev and new focal, consc	Yes	Herniation (diffuse edema)
26	Heparin, mechanical thrombolysis	Antiosmotics, pentothal	Prev focal	Yes	Herniation (M inf and edema)
27	Antiplatelets	ACV	Mental, new focal, consc, seizure	Yes	Herniation (hem)

LMWH indicates low-molecular-weight heparin; ACV, anticonvulsants; mental, mental disorder; prev, worsening of previous deficit; consc, decreased consciousness; NK, not known; hem, hemorrhage; M, multiple; inf, infarct; HIV, human immunodeficiency virus; NPE, neurogenic pulmonary edema; PE, pulmonary embolism. Other abbreviations are as defined in text.

come in the predictor. The variables retained in this model were seizure, mental status disorder, GCS <9 at admission, deep CVT, posterior fossa lesion, worsening of focal signs, or occurrence of new focal signs after admission. (Table 3).

Discussion

ISCVT is the largest prospective series of patients with CVT collected in different centers and countries. The most common cause of death was transtentorial herniation due to a unilateral hemorrhagic lesion or diffuse edema and bilateral lesions. Main predictors of death within 30 days were seizure, mental status disturbances, coma (GCS <9), deep CVT, and right hemorrhage and posterior fossa lesions.

ISCVT reported a lower case fatality than the majority of previous studies, including those performed in specific settings such as pregnancy or puerperium. Table 4 depicts

the percentages of death and their 95% CIs in recent case series of CVT with >20 patients.^{7,11–12,16–29} To decrease potential ascertainment bias in ISCVT, investigators were repeatedly asked to search for cases through the Imaging Department, Intensive Care Unit, and other hospital departments.

Causes of death were not addressed systematically previously. Early autopsy series gave details about the location of occluded veins and sinus and parenchymal lesions, but overall they did not provide the cause of death. Pulmonary embolism, heart disease, cachexia and marasmus, and intracranial lesions were considered the cause of death in autopsy studies.^{2–5} Many cases were associated with infectious diseases, which are currently less common. We have identified only 1 case of death due to pulmonary embolism, which is less than previously suggested,³⁰ probably because of the generalized treatment with heparin in ISCVT patients. Death

TABLE 3. Predictors of Death in Multivariate Analysis

Predictors	n/N, %	OR	95% CI	P
At admission				
Any seizure	15/245, 6.1	5.4	1.5–19.7	0.010
Mental status disorder	12/137, 8.8	2.5	0.9–7.3	0.097
GCS <9	8/31, 25.8	8.8	2.8–27.7	0.000
DVS thrombosis	9/68, 13.2	8.5	2.6–27.8	0.000
Lesion posterior fossa	4/26, 15.4	6.5	1.3–31.7	0.021
Right intracranial hemorrhage	10/113, 8.8	3.4	1.1–10.6	0.036
Sensitivity=16%, specificity=100%; area under the receiver operating characteristic curve=0.91; 95% CI 0.86–0.97				
Predictors at admission and during clinical course				
Any seizure	15/245, 6.1	4.6	1.3–16.6	0.020
Mental status disorder at admission	12/137, 8.8	3.4	1.0–11.0	0.044
GCS <9 at admission	8/31, 25.8	13.1	3.8–45.4	0.000
DVS thrombosis	9/68, 13.2	4.1	1.1–14.7	0.032
Lesion posterior fossa	4/26, 15.4	6.1	1.1–33.5	0.036
Worsening of focal sign	10/46, 21.7	5.3	1.5–18.9	0.011
New focal sign	8/43, 18.6	4.6	1.2–17.8	0.000
Sensitivity=26%, specificity=99.7%; area under receiver operating characteristic curve=0.94; 95% CI 89–0.98				

n indicates No. of patients with the outcome and predictor; N, total patients with the predictor; and DVS, deep cerebral venous system thrombosis. Other abbreviations are as defined in text.

could have been due to pulmonary embolism in another patient with sudden death and respiratory distress, although this was not confirmed.

In more recent series of CVT, causes of death were seldom ascertained. In the VENOPORT study, cerebral edema with or without seizures, cerebral anoxia due to seizure, and

sudden cardiopulmonary arrest were the major causes of death.¹¹ Other series reported transtentorial herniation due to hemorrhagic infarct,³¹ intubation accident leading to cardiopulmonary arrest,³¹ and septic multiorgan failure.²¹ In the present study, the main causes of death were neurologic, most frequently transtentorial herniation, due to either focal hemorrhagic lesion or multiple lesions with diffuse edema. This distinction may be important when selecting therapy for individual patients. Decompressive craniectomy was recommended for such patients many years ago⁵; however, this intervention has only rarely been reported in recent years.³² In light of our findings, decompressive craniectomy should be reconsidered for patients with progressive herniation.

Several models predicting the outcome “death or dependency” have been reported,^{10,24,33} but no predictive model of death has been previously described. The individual time course is highly variable in venous stroke. This partly explains why our predictive model has a low sensitivity. By adding “clinical course after admission” to admission variables, we identified more patients at high risk of death, such as those developing new focal signs or showing a worsening of a previous focal deficit. However, there are still limitations in predicting individual survival outcome.

The results of this study have important implications. First, although CVT has a low case fatality, it is possible to predict some patients who are at increased risk of death. These patients should be closely monitored, and worsening of their clinical condition should be regarded as an indication for more aggressive treatment. Second, given the potential for neurologic recovery after CVT, there is a case for assessing decompressive craniectomy in patients who are deteriorating due to a parenchymal lesion producing a mass effect.

TABLE 4. Case Fatality in Recent Case Series of CVT

First Author and Reference No.	Year		Died, No.	Died, %	95% CI
	Published	Total			
Einhäupl ¹⁶	1991	71	10	14	8–24
Ameri ¹⁷	1992	110	6	6	3–11
Barinagarrementeria ¹⁸	1992	78	18	23	15–34
Cantu ⁷	1993	46	15	33	21–47
Daif ¹¹	1995	40	4	10	4–23
Brucker ²⁰	1998	42	1	2	0.4–12
Bergui ²¹	1999	26	2	8	2–24
De Bruijn ²²	2001	59	6	10	5–21
Ferro ¹¹	2001	142	9	6	3–12
Baumgartner ²³	2003	33	0	0	0–10
Breteau ²⁴	2003	55	2	4	1–12
Mehraein ²⁵	2003	79	8	10	5–19
Soleau ²⁶	2003	31	5	16	7–33
ISCVT ¹²	2004	624	27	4	3–6
Pregnancy or puerperium					
Sanchetee ²⁷	1992	25	3	12	4–30
Cantu ⁷	1993	67	6	9	4–18
Hamouda-M'Rad ²⁸	1995	33	12	36	22–53
Nagaraja ²⁹	1999	150	26	17	11–25
ISCVT ¹²	2004	77	3	4	1–11

Abbreviations are as defined in text.

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