Natural history of cerebral vein thrombosis: a systematic review

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Cerebral vein thrombosis (CVT) has been considered, until a few years ago, an uncommon disease with significant long-term morbidity and high mortality rate. New noninvasive diagnostic techniques have increased the frequency with which this disease is diagnosed; despite this, there continues to be little data on its natural history. The objectives of this study were to evaluate the mortality rate, the rate of disability at long-term follow-up, and the incidence of recurrence after a first episode of CVT; to determine clinical and radiologic predictors of death and dependence; and to identify possible risk factors for recurrence. (Data source: MEDLINE and EMBASE databases, reference lists of selected articles and authors' libraries.) Nineteen studies were identified. Mortality rate during peri-hospitalization period is 5.6% (range, 0%-15.2%) and 9.4% (range, 0%-39%) at the end of follow-up period. Eighty-eight percent of surviving patients recover completely or have only a mild functional or cognitive deficit. Two thirds of patients with CVT recanalized within the first few months after presentation, and 2.8% (range, 0%-11.7%) had objectively confirmed recurrence. We conclude that patients with CVT have a low risk of death and that most patients have a good long-term prognosis. (Blood. 2006;108:1129-1134)

Introduction

Cerebral vein thrombosis (CVT) is a rather uncommon disease. However, the recent introduction of noninvasive and highly sensitive diagnostic techniques such as magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) has modified our knowledge of the spectrum of illness associated with CVT. The ability to accurately detect less clinically severe cases of CVT has modified the "natural history" of this disorder. Thus, in contemporary series, the reported mortality rate ranges between 8% and 14%,[1-4] in contrast to prior studies within which cause-specific mortality was as high as 30% to 50%.[5] Although some patients with CVT present with catastrophic complications, such as a stroke syndrome with focal neurologic signs or coma, many present with mild or nonspecific symptoms, such as isolated intracranial hypertension, presenting with headache and papilledema.[1-4,6,7] However, conversely to arterial stroke, scarce information exists on natural history and long-term prognosis of CVT. Existing studies often are limited by small numbers, their retrospective nature, and short follow-up. In an effort to better understand the natural history of CVT, we performed a systematic research on the existing literature. Our aims were to evaluate the acute and long-term mortality rate of patients with CVT, to evaluate clinical outcomes and the rate of disability over long-term follow-up, to determine clinical and radiologic predictors of death and dependence, to estimate the cumulative incidence of recurrent CVT after a first episode of CVT, and to identify possible risk factors for recurrent CVT.

Patients, materials, and methods

A computer-assisted search was performed to identify all published studies that evaluated the natural history of CVT. Studies were identified using MEDLINE (from 1966 to October 2005) and EMBASE (from 1980 to October 2005) databases. All searches were carried out without any language restriction, using free text and medical subject headings. The following search terms were used and combined: cerebral vein thrombosis, cerebral venous thrombosis, intracranial embolism or thrombosis, cerebral veins, intracranial thrombosis, sinus thrombosis intracranial, follow-up, follow-up studies. The list of articles was manually reviewed by 2 authors (M.G., F.D.). Papers whose titles or abstracts suggested they met inclusion criteria were selected for detailed review.

Studies were included when they fulfilled the following a priori defined inclusion criteria: (1) they contained original data; (2) diagnosis of CVT was objectively confirmed (with digital substraction or conventional angiography, magnetic resonance imaging, or magnetic resonance angiography, computed tomography venography, at surgery or with autopsy); (3) patients were 18 years or older; (4) studies included at least 10 patients; (5) studies had a follow-up of at least 3 months; (6) studies provide information on one or more of the following data: mortality and disability rates, clinical or radiologic predictors of poor outcome, recanalization, or recurrence of CVT.

Additional papers meeting these inclusion criteria were selected for review from the authors' libraries and from review of the reference lists of those articles selected for detailed review.

We excluded all studies in which the diagnosis of CVT was exclusively clinical without objective imaging and all the studies in which residual disability was not measured clearly or with a commonly accepted score (ie, modified Rankin Score, Glasgow Outcome Scale). When multiple papers for a single study had been published, we used the latest publication, and we supplemented it, if necessary, with data from earlier publications.

For each study selected, 2 reviewers (M.G., F.D.) independently and in duplicate extracted data on study characteristics and the following outcomes: mortality, residual disability, recanalization, recurrence, and potential radiologic and clinical predictors of poor outcome. Acute mortality was defined as occurred in the first 30 days from diagnosis. Disagreement was resolved by consensus or by opinion of a third reviewer (W.A.).

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Patients with a modified Rankin Score (mRS) ranging between 0 and 2 or with a Glasgow Outcome Scale (GOS) ranging between 1 and 2 were considered to have a favorable outcome, whereas patients with an mRS between 3 and 5 or survived patients with a GOS between 3 and 5 were considered to have a poor outcome.

Because the use of quality scoring systems in observational studies is controversial,[8] we assessed study quality considering 2 characteristics. First, we considered the study design: prospective cohort studies were judged to be of higher quality compared to retrospective cohort studies. Second, we considered the enrollment: studies in which the enrollment of patients was consecutive were considered to be of higher quality than studies in which the enrollment was not consecutive. A formal combined meta-analysis of these studies was not appropriate due to the heterogeneity of methodology and outcome assessments among the trials, and therefore, a narrative synthesis of collected data was undertaken. Data are presented as mean, percentage, and range of variation.

Results

Study characteristics

Using our search strategy, we identified 812 studies. Twenty-two studies met inclusion criteria.[1,4,9-28] Three studies were extracted from 2 different publications; therefore, 19 studies were included in our systematic review[4,9,11-18,20-28] and supplemented with data of 3 other publications.[1,10,19] The main characteristics of the studies included in our systematic review are summarized in Table 1. Of 19 included studies, 16 were written in English[4,9,11-18,20-22,24,27,28] and 1 each was written in French,[25] Spanish,[23] and Dutch.[26] A total of 1488 patients were included in our analysis. Studies ranged in size from 13 to 624 patients. CVT was diagnosed with CTA, MRI, MRA, or contrast angiography in all studies. Excluding the trial of de Bruijn et al,[4,19] in which 30 of 60 patients included in the study were randomized to placebo, almost all the other patients included in our systematic review have received unfractionated or low-molecular-weight heparin for at least 5 days, followed by oral anticoagulation for at least 3 to 6 months. One randomized controlled trial and 5 prospective and 12 retrospective studies were included in our systematic review. Furthermore, 2 contained both retrospective and prospective data. Thirteen enrolled patients consecutively.[4,9,12,14-16,20-22,24,25,27,28] Mortality was evaluated in 15 studies.[4,9,11-14,16,18,20,21,23-28] Clinical outcome and residual disability after CVT were examined in 16 studies.[4,9,11-14,16-18,20,21,23-28] In all but 4 studies the functional clinical outcome was assessed with the modified mRS at 3 to 6 months or at 1 year or more.[4,9,11,12,14,16,18,20,21,23,24,27] The mRS was classified, in most of the reports, as complete recovery (mRS 0 to 1), partial recovery, independent (mRS 2), dependent (mRS 3 to 5), and death (mRS 6). Some studies used mRS with a different classification. One evaluated the outcome with GOS,[25] and 3 did not use a specific scale to evaluate patients at follow-up.[17,26,28] The mean follow-up was 3 months in 3 studies[11,14,26] and 6 months or more in the other reports[4,9,12,13,16-18,20,21,23-25,27,28] (range, 6 months to 10.25 years). Five studies considered recanalization rate,[10-14,17] and 2 evaluated the influence of recanalization on clinical outcome.[10,17] The recurrence of CVT was evaluated in 12 studies,[9,12,13,15-17,20-22,24,25,27] 6 of which evaluated the recurrence of CVT during subsequent pregnancies.[15,16,21,22,24,27] Clinical or radiologic predictors of outcome were found in 10 studies.[4,9,16,18,21,23,25-28] There were no studies that had evaluated risk factors for recurrence of CVT.

Mortality

Data on acute and total mortality are shown in Table 2. The mortality rate during the acute phase was assessed in 12 studies.[4,9,11,12,14,16,21,23-25,27,28] Of 1180 evaluated patients, 66 died within the first month (mean, 5.6%; range, 0%-15.2%). However, the mortality rate varied highly between the studies and was 0 in 5 studies. Of 45 evaluated patients, 32 died as a consequence of CVT (most of them for cerebral herniation), whereas most of 13 died as a consequence of an underlying disease. The overall mortality rate at the end of follow-up was 9.4% (122 deaths in 1303 total patients). However, it was highly

Table 1. Baseline characteristics

Study, year	Patients, no.	Mean or median follow-up, mo	Study design	Consecutive enrollment	Lost at follow-up, no.
Appenzeller et al,[28] 2005	24	44	Retrospective	Yes	0
Stolz et al,[9,10] 2005	79	31	Prospective, retrospective	Yes	2
Ferro et al,[1,27] 2005	624	16	Prospective	Yes	8
Favrole et al,[11] 2004	28	3	Retrospective	No	0
Cakmak et al,[14] 2003	16	3	Prospective	Yes	0
Breteau et al,[21] 2003	55	36	Retrospective	Yes	0
Mehraein et al,[15] 2003	39	123	Retrospective	Yes	NA
Baumgartner et al,[12] 2003	33	12	Prospective	Yes	0
Buccino et al,[13] 2002	36	42	Retrospective	No	1
Ferro et al,[16] 2002	142	22	Prospective, retrospective	Yes	7
Strupp et al,[17] 2002	40	145	Retrospective	No	NA
Fink and McAuley,[18] 2001	25	10.8	Retrospective	No	0
Mak et al,[20] 2001	13	5-36*	Retrospective	Yes	0
de Bruijn et al,[4,19] 2001	59	18.5	Retrospective	Yes	4
Lamy et al,[22] 2000	68	60	Prospective	Yes	NA
Lleo et al,[23] 1999	17	26.33	Retrospective	No	0
Preter et al,[24] 1996	110	77.8	Retrospective	Yes	25
Rondepierre et al,[25] 1995	18	31	Prospective	Yes	0
Bienfait et al,[26] 1995	62	3	Retrospective	No	0

NA indicates not assessed.
*Range.

Table 2. Mortality rate, disability at 3 to 6 months and at 1 year or more

Study, year	No. of patients	Acute death, no. (%)	Total death, no. (%)	Outcome at 3 to 6 mo, no. patients			Outcome at 1 y or more, no. patients		
				Tot	Death	Level of disability	Tot	Death	Level of disability
Appenzeller et al,[28] 2005	24	0 (0)	0 (0)	NA	NA	NA	24	0	Complete recovery: 13; neurologic impairment: 11
Stolz et al,[9,10] 2005	79	12 (15.2)	14 (17.7)	62	0	mRS 0–1: 54; mRS 2–3: 4; mRS 4–5: 4	58	2	mRS 0–1: 50; mRS 2–3: 2; mRS 4–5: 4
Ferro et al,[1,27] 2005	624	27 (4.3)	52 (8.3)	589	15	mRS 0–1: 481; mRS 2: 49; mRS 3–5: 44	582	10	mRS 0–1: 493; mRS 2: 47; mRS 3–5: 32
Favrole et al,[11] 2004	28	0 (0)	0 (0)	28	0	mRS 0–1: 26; mRS 2: 1; mRS 4: 1	NA	NA	NA
Baumgartner et al,[12] 2003	33	0 (0)	0 (0)	NA	NA	NA	33	0	mRS 0–2: 27; mRS > 2: 6
Buccino et al,[13] 2003	36	NA	1 (2.8)	NA	NA	NA	35	1	mRS 0–1: 34
Cakmak et al,[14] 2003	16	0 (0)	0 (0)	16	0	mRS 0–1: 9; mRS 2: 5; mRS 3–5: 2	NA	NA	NA
Breteau et al,[21] 2003	55	4 (7.3)	7 (12.7)	NA	NA	NA	51	3	mRS 0–2: 45; mRS 3–5: 3
Ferro et al,[16] 2002	142	9 (6.3)	11 (7.7)	NA	NA	NA	126	2	mRS 0–1: 108; mRS 2: 12; mRS 3–5: 4
Strupp et al,[17] 2002	40	NA	NA	NA	NA	NA	40	NA	Complete or partial recovery: 29; focal neurologic deficits: 11
Fink and McAuley,[18] 2001	25	NA	1 (4)	NA	NA	NA	25	1	mRS 0–1: 16; mRS 2: 7; mRS > 3: 1
de Bruijn et al,[4,19] 2001	59	6 (10.2)	8 (13.6)	53	0	mRS 0–2: 49; mRS > 3: 4	49	2	mRS 0–1: 25; mRS 2–3: 19; mRS > 3: 3
Lleo et al,[23] 1999	17	0 (0)	2 (11.8)	17	2	mRS 0–2: 10; mRS 3–5: 5	NA	NA	NA
Preter et al,[24] 1996	85	6 (7.1)	8 (9.4)	79	2	NA	77	0	mRS 0–1: 66; optic atrophy: 2; seizure alone: 4; neuropsychiatric disturbance: 3; hemispheric deficit: 1; multiple cn palsies, cerebellar incoordination: 1
Rondepierre et al,[25] 1995	18	2 (11.1)	7 (39)	16	5	GOS 1–2: 10; GOS 3–5: 1	NA	NA	NA
Bienfait et al,[26] 1995	62	NA	11 (17.7)	62	11	mRS 0–2: 41; mRS 3–5: 10	NA	NA	NA

mRS indicates modified Rankin Score; GOS, Glasgow Outcome Scale; NA, not assessed; Tot, total number of evaluable patients at each follow-up visit; Death, total number of patient deaths at each follow-up visit; and Level of disability, number of patients with different levels of disability.

variable between the studies (range, 0%-39%). Noteworthy, most of the deaths that occurred during follow-up were related to an underlying condition such as cancer (24 of 38 evaluated deaths during follow-up), and they were not a direct consequence of cerebral vein thrombosis.

Disability

Outcome information was available for 8 studies at 3 to 6 months of follow-up[4,9,11,14,23,25-27] and 11 studies at one or more years of follow-up[4,9,12,13,16-18,21,24,27,28] (Table 2). Eight hundred and forty-three patients provided data at 3 to 6 months of follow-up; 735 surviving patients (87.2%; range, 58.9%-96.4%) had a good outcome with complete or partial recovery, and 73 patients (8.7%; range, 3.6%-29.4%) had a poor outcome with permanent neurologic deficits. At 12 or more months, 12 studies evaluated 1100 patients. Among these, 972 (88.3%; range, 54.2%-97.1%) had a complete or partial recovery, and only 107 (9.7%; range, 0%-45.8%) had a poor outcome.

Recanalization

Five studies investigated the recanalization of cerebral venous thrombosis[10-12,14,17] (Table 3). Unfortunately, all these studies presenting data on recanalization have a relatively small sample size (ranging from 16 to 40 patients) and, in total, enrolled 154 patients. Four of these defined recanalization as complete (blood flow without any interruption), partial (small interruption of continuous blood flow and/or narrowing of the venous lumen), or absent (interrupted blood flow), and the other did not distinguish between partial and complete recanalization.[14] Recanalization was evaluated at 3 to 6 months in 4 studies,[10-12,14] at 1 year in 3

Table 3. Recanalization at 3 to 6 months and at 1 year or more

Study, year	No. of patients	Partial recanal at 3 to 6 mo, no.	Complete recanal at 3 to 6 mo, no.	Partial recanal at 1 y or more, no.	Complete recanal at 1 y or more, no.
Stolz et al,[10] 2004	37	7	19	7	20
Favrole et al,[11] 2004	28	7	16	NA	NA
Baumgartner et al,[12] 2003	33	15	18	15	18
Strupp et al,[17] 2002	40	NA	NA	12	21
Cakmak et al,[14] 2003	16	12*	NA	NA	NA

NA indicates not assessed.

*The authors of this study did not distinguish between partial and complete recanalization.

Table 4. Recurrence of CVT and predictors of poor outcome

Study, year	Predictors of poor outcome	Recurrent CVT, no./ no. total patients (%)	Other VTE events, no./ no. total patients (%)
Appenzeller et al,[28] 2005	Parenchymal involvement: OR, 67.8; CI, 2.12–132.86 (hemorrhagic or ischemic) Thrombophilia or systemic disease: OR, 14.4; CI, 1.35–152.62	0/24 (0)	0/24 (0)
Stolz et al,[9,10] 2005	Age: $P < .01$ NIHSS upon admission: $P < .01$ At least 2 seizures during hospital treatment despite antiepileptic treatment: $P < .01$ Venous infarct: $P < .01$ Intracranial hemorrhage: $P < .01$	2/58 (3.4)	5/58 (8.6)
Ferro et al,[1,27] 2004	Older than 37: HR, 2.00; CI, 1.23–3.27 Male sex: HR, 1.59; CI, 1.01–2.52 Any malignancy: HR, 2.90; CI, 1.60–5.08 CNS infection: HR, 3.34; CI, 1.98–17.24 Any seizure: OR, 6.1; CI, 1.3–16.6 Mental status disorder: OR, 3.4; CI, 1.0–11.0 GCS less than 9 at admission: OR, 13.1; CI, 3.8–45.4 DVS thrombosis: OR, 4.1; CI, 1.1–14.7 Lesion posterior fossa: OR, 6.1; CI, 1.1–33.5 Worsening of focal sign: OR, 5.3; CI, 1.5–18.9 New focal sign: OR, 4.6; CI, 1.2–17.8	14/572 (2.4)	19/572 (3.3)
Breteau et al,[21] 2003	Neurologic deficit at time of diagnosis: $P = .03$ Cancer and malignant hemopathy: $P = .038$ Impaired consciousness: NS Cerebral hemorrhage: NS	0/48 (0)	3/48 (6.3)
Baumgartner et al,[12] 2002	NA	0/33 (0)	0/33 (0)
Buccino et al,[13] 2002	NA	1/34 (2.9)	NA
Ferro et al,[16] 2002	Coma: HR, 1.21; CI, 0.75–1.95 Worsening after admission: HR, 1.17; CI, 0.85–1.62 Aphasia: HR, 1.40; CI, 0.94–2.07	2/124 (1.6)	3/85 (3.5)
Strupp et al,[17] 2002	NA	0/40 (0)	NA
de Bruijn et al,[19] 2001	Coma: OR, 8.2; CI, 1.3–50.1 Intracranial hemorrhage: OR, 20.7; CI, 1.6–264.3 Involvement of straight sinus: NS Impaired consciousness: NS	NA	NA
Mak et al,[20] 2001	NA	0/13 (0)	NA
Lleo et al,[23] 1999	Impaired consciousness, cancer	NA	NA
Preter et al,[24] 1996	NA	9/77 (11.7)	NA
Bienfait et al,[26] 1995	Coma: RR, 3.5 Hemiparesis at time of diagnosis: RR, 2.3	NA	NA

VTE indicates venous thromboembolic; NA, not assessed; OR, odds ratio; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; CNS, cerebral nervous system; GCS, Glasgow Coma Scale; DVS, deep vein thrombosis; NS, not significant; and RR, relative risk.

studies,[10,12,17] and at both time points in 2 studies.[10,12] If the rates of recanalization presented in these studies are combined numerically, there was no difference in the rate of recanalization at 3 months and at one year of follow-up (59 of 70 [84%] at 3 months and 60 of 70 [85%] at 1 year). These results suggest that recanalization occurs only within the first months following CVT and not thereafter, irrespective of anticoagulation. No correlation between recanalization and clinical outcome was found in the 2 studies that examined this relationship.[10,17]

Recurrence

The overall recurrence rate was presented in 13 studies. In these studies, 2.8% (29 new instances of CVT in 1048 patients evaluated; range, 0%-11.7%) patients experienced a recurrence[9,12,13,15-17,20-22,24,25,27,28] (Tables 4,5). Duration of follow-up varied widely between studies, ranging from 12 to 145 months. In their prospective study, Ferro et al[27] evaluated recurrences in 624 adults with a previous episode of CVT. Fourteen subjects (2.2%)

Table 5. Recurrence of CVT and predictors of good outcome

Study, year	Predictors of good outcome	Recurrent CVT, no./ no. total patients (%)
Ferro et al,[2,27] 2004	Isolated intracranial hypertension at time of diagnosis: HR, 0.45; CI, 0.23–0.87	14/572 (2.4)
Breteau et al,[21] 2003	Isolated intracranial hypertension at time of diagnosis: $P < .001$	NA
Rondepierre et al,[25] 1995	Isolated intracranial hypertension at time of diagnosis: $P = .06$ Young age: $P = .06$	1/18 (5.5)

No other VTE events were recorded.
VTE indicates venous thromboembolic; HR, hazard ratio; and NA, not assessed.

had a recurrent sinus thrombosis over 16 months of follow-up. Almost half (41.5%) of the recurrences occurred during anticoagulant treatment. On the other hand, Preter and colleagues[24] reported a much higher risk of recurrence: in their study, 9 of 77 (11.7%) patients had recurrent CVT.

Data on the incidence of other thromboembolic events (apart from CVT) were presented only in 6 studies[10,12,16,21.27,28]; in these studies there were 30 events in 819 evaluated patients (3.7%; range, 0%-8.62%).

Six studies assessed the risk of recurrence of CVT during subsequent pregnancy and puerperium[15,16,21,22,24,27] (Table 6). There was only 1 recurrence in 103 pregnancies (0.97%; range, 0%-2.9%); however, spontaneous abortion was a frequent complication in these patients.

Predictors of outcome

Ten studies evaluated the predictors of poor or of good outcome[4,9,16,18,21,23,25-28] (Tables 4,5). Using multivariate analysis, Ferro and colleagues[27] found that age of more than 37 years, male sex, coma, seizure, mental status disorder, deep CVT, right intracranial hemorrhage, posterior fossa lesion, worsening of previous focal or de novo focal deficits, cerebral nervous system infection, and cancer were predictors of death or dependence. Cancer, coma, and intracranial hemorrhage were confirmed as predictors of poor outcome in other studies.[4,16,21,23,26] On the other hand, isolated intracranial hypertension at the time of diagnosis was found to be a predictor of good outcome in 3 studies.[21,25,27] Noteworthy, Appenzeller et al[28] found that presence of parenchymal involvement (hemorrhagic or ischemic) on CT or MRI was associated with an increased risk of developing neurologic sequelae.

Discussion

Our study confirmed that most patients with cerebral vein thrombosis have a more benign prognosis than previously suspected: 5.6% of patients died during the acute phase, and 9.4% of patients had died at the end of the follow-up period. Conversely to the acute phase, where most patients died due to cerebral herniation, during the follow-up period most patients had died due to underlying conditions such as cancer rather than as a result of direct consequences of their CVT. Most surviving patients recovered completely or had only mild functional or cognitive deficit; less than 1 in 5 surviving patient was dependent or had a permanent disability at the end of the follow-up period. Patient characteristics likely to be associated with an adverse outcome include: age older than 37; presence of focal deficits at presentation; altered consciousness, including coma, at presentation; intracranial hemorrhage; involvement of cortical veins; and underlying cancer. More than two thirds of patients with CVT had partial or complete recanalization within the first few months after presentation: there was no evidence that recanalization occurred between 3 and 6 months after presentation. However, the potential benefit of a complete recanalization on the short- or long-term outcome remains unknown. Recurrences of CVT after a first episode are uncommon, occurring in 2.8% of patients. Young women, who developed CVT during pregnancy or puerperium, have a low risk of recurrence during subsequent pregnancies.

Our results confirm that CVT is a more benign disease than previously considered. This is likely due to several facts. First, more sensitive diagnostic techniques have undoubtedly led to the detection of smaller thrombi, which likely have better prognosis. Second, older series had patients with infection-associated CVT; such events are very rare since the advent of antibiotics. Third, widespread treatment of CVT with anticoagulation probably has changed the natural history of this disease.

Our observations confirm that the natural history of CVT is different from that of arterial stroke. About 10% of stroke patients die during hospitalization,[29] approximately 20% die within one year of discharge,[30] and about 35% of the hospitalized stroke survivors with motor deficits of the legs do not show any degree of motor recovery.[31] Only one of 4 stroke patients presents a complete neurologic recovery during follow-up.[32] Furthermore, the incidence of recurrent events is dramatically lower following CVT as compared to arterial cerebrovascular diseases and to venous thrombosis occurring in other sites. Indeed, about 4% of stroke patients experience a recurrence every year, with a cumulative risk of recurrence at 10 years of 43%.[33]

Our systematic review has limitations. First, although the number of patients lost at follow-up was generally low, we cannot exclude case-ascertainment bias in the underlying studies. The risk of this bias is increased by the fact that our analysis was limited to observational studies, some of which were retrospective. Second, mortality, residual disability, and rate of recurrence varied widely between the studies, suggesting some differences in populations examined. Third, although we obtained data on anticoagulant treatment for almost all studies, it was not possible to know, in many cases, whether the patients who suffered a recurrence were receiving anticoagulants and if they were treated adequately at the time of recurrence. Finally, although we collected data from 19 studies and from more than 1400 patients, the total number of deaths and recurrences remained low, not allowing definitive conclusions on these particular topics. However, the results of our systematic review are relevant because they add important knowledge to the natural history of cerebral vein thrombosis. Prior to this systematic review, information on the natural history of the disease was rather inconclusive. Indeed, to date, only 3 studies that have included more than 100 patients have been published.

Table 6. Recurrence rate of CVT during pregnancy and puerperium

Study, year	No. of pregnancies	No. of miscarriages	No. of uneventful pregnancies	No. of Recurrences
Ferro et al,[2,27] 2005	34	4 spontaneous, 5 voluntary	21	1
Mehraein et al,[15] 2003	22	2 spontaneous, 1 induced abortion	19	0
Breteau et al,[21] 2003	3	1 spontaneous	2	0
Ferro et al,[16] 2002	2	0	2	0
Lamy et al,[22] 2000*	187	30 spontaneous, 37 voluntary	115†	0
Preter et al,[24] 1996	16	2 spontaneous, 2 voluntary	12	0

*Lamy and colleagues provided data of subsequent pregnancies in patients with previous cerebral vein thrombosis and arterial stroke.
†26 CVT patients.

Other important aspects of CVT, such as risk factors and optimal treatment, have not been addressed in our systematic review. The first issue was recently covered by our group in a meta-analysis, which showed that users of oral contraceptives and patients with factor V Leiden, the prothrombin G20120A mutation, and hyperhomocysteinemia are at significantly increased risk of CVT.[34] There are few good quality clinical trials published on the treatment of cerebral vein thrombosis,[35,36] limiting the quality of a systematic review of treatment for this disorder.

In conclusion, we found that about 85% of patients with CVT survive and that the majority of survivors have an excellent long-term outcome. Altered level of consciousness at presentation, intracranial hemorrhage, and an underlying cancer are important adverse prognostic factors. Relapses are rare, but other thromboembolic events are not infrequent in these patients.

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