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Risk factors associated with recurrent venous thromboembolism after a first cerebral venous thrombosis event: A cohort study

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ABSTRACT

Background: Cerebral venous thrombosis (CVT), although rare, is potentially fatal. Few studies have investigated risk factors associated with recurrent venous thromboembolism (VTE) after a first CVT event of which most are from Caucasian populations. The aim of this study was to evaluate risk factors associated with recurrent VTE after a first CVT event in a South American-population.

Patients/methods: In this cohort, multicenter study, patients aged > 18 years and objectively-diagnosed with CVT were included, with follow-up starting after discontinuing anticoagulant therapy. The primary outcome was symptomatic VTE recurrence at any venous site.

Results: We included 203 patients with a median age of 30.8 (interquartile range [IQR], 24.7–40.9) years and a follow-up of 3.0 (IQR, 1.2–5.6) years. Most patients (86.2%) were women, and among those of reproductive age (n = 162), 65.4% developed CVT during oral contraceptive use, and 9.2% during pregnancy/puerperium. Thirteen patients (6.9%) developed VTE recurrence after a first CVT, yielding an overall rate of 1.6/100 patient-years (95% confidence interval [CI], 0.8–2.8). Recurrence rate was higher in males (4.6/100 patient-years; 95% CI, 1.2–11.7) than in females (1.2/100 patient-years; 95% CI, 0.6–2.4), and in patients with factor V Leiden mutation (9.2/100 patient-years; 95% CI, 1.1–33.1) than in those without it (1.2/100 patient-years; 95% CI, 0.5–2.4).

Conclusions: VTE recurrence after a first CVT was low. In spite of the limitation of small sample size, male sex and factor V Leiden mutation were the only factors associated with a significant higher risk of recurrent VTE after a first CVT in a multivariate analysis.

1. Introduction

Cerebral venous thrombosis (CVT) is a rare vascular disease of the brain which is characterized by the occlusion of venous sinuses and/or cerebral veins by thrombi. CVT accounts for < 1% of all strokes and mainly affects young adults and children [1]. The estimated annual incidence of CVT is seven cases per million neonates/children and three to four cases per million adults [2,3]. A recent study reported an incidence of 1.32 cases per 100,000 adult patients/year [4].

CVT occurs more frequently in women [3,5]. The main risk factors associated with CVT are cerebral tumors, infection, trauma, arteriovenous malformation, use of oral contraceptives, pregnancy, puerperium, and inherited thrombophilia. The etiology of CVT remains unknown in 15%–20% of cases [2,5,6].

Few studies have assessed factors associated with the risk of venous thromboembolism (VTE) recurrence after a first CVT event [2,7,8]. In all these studies, the population studied almost completely consisted of European and North American individuals. Since ethnicity appears to influence the risk for VTE, and the prevalence of prothrombotic mutations varies in different populations [9,10], evaluating the risk factors for VTE recurrence after a first CVT in other populations is an important step to better understand this rare vascular disease. This may target groups who might benefit from specific medical advice and care.

This study aims to assess the risk factors associated with VTE recurrence after a first CVT event in a population of patients from Southeastern Brazil.

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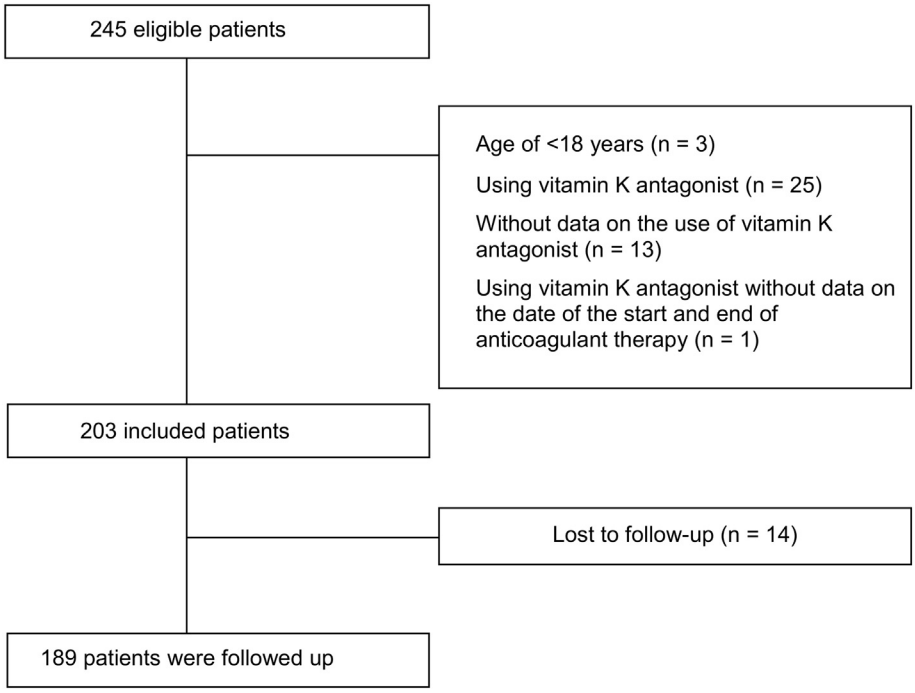

Fig. 1. Flow chart of patients included in the study.

2. Methods

2.1. Study design and setting

This is a multicenter, prospective cohort study. Patients were recruited from the four centers, belonging to two states, located in Southeastern Brazil.

2.2. Participants

The inclusion criteria comprised adult patients (≥18 years) diagnosed with symptomatic and objectively-confirmed CVT as the first and unique event. Objective methods included magnetic resonance imaging (MRI), computed tomography (CT), and/or cerebral angiography. Patients were excluded if (i) the first event of CVT was not objectively-confirmed, (ii) the patient had recurrent VTE, (iii) there was contraindication for discontinuation of anticoagulation at the moment of the inclusion in the study, and (iv) if the VTE was not objectively-confirmed.

Patients were consecutively included between April 1, 2000 and June 30, 2014. There was no selection over the referral of patients to the participating centers. Data were collected by trained hematologists by using standardized methodology by all centers. A standardized questionnaire was used to collect data at admission and at follow-up visits. A telephone interview was conducted by a healthcare professional for those patients who did not attend the follow-up visit. For this, a standardized questionnaire was used. Upon information of a recurrence or suspected recurrence an appointment was made with the physician/researcher to confirm the recurrence by clinical examination and objective methods. The patients were advised to contact the physician/researcher if they presented symptoms of a suspected thrombotic event.

The follow-up period started after discontinuing the anticoagulation therapy and ended at the time of recurrence, last appointment, or last contact. As the last patient was included in June 30, 2014, the date of January 15, 2015 was established as the earliest date for reassessing all patients. The rational for this was to ensure a minimum follow-up of 6 months after discontinuing vitamin K antagonist (VKA) therapy. If a patient was unable to attend the medical appointment nor answered the telephone call after this date, the follow-up time mentioned was not the same as the specific single date for all patients, but rather the date of last contact with the patient.

Informed consent was obtained for included patients. The study was approved by the Ethics Committees of participating centers.

2.3. Variables

The following variables were analyzed: age, sex, data on first CVT (date of diagnosis, date of CVT confirmation by objective method, risk factors, factor V Leiden mutation, prothrombin G20210A mutation, oral anticoagulant used, and start and end dates of anticoagulation), follow-up data (date of the first visit and date of last contact with the patient), and data related to VTE recurrence, when applicable (date of the event, age at the time of event, affected site, date of confirmation of the event by objective methods, and risk factors associated with VTE recurrence).

An unprovoked event was defined as VTE which occurred in the absence of any known risk factors for VTE. A provoked event was defined as a VTE which occurred in association with at least one known risk factor for VTE. Risk factors for VTE were oral contraceptive use, hormone replacement therapy, pregnancy, puerperium, hospitalization for clinical reasons (hospitalization for > 3 days in the last 3 months), surgery, dehydration, nephrotic syndrome, vasculitis (systemic lupus erythematosus, Behçet's disease, rheumatoid arthritis, thromboangiitis obliterans, non-specified), other inflammatory systemic disorders (intestinal inflammatory disease, sarcoidosis), local or systemic infection (central nervous system [CNS], ear, sinus, mouth, face, cellulitis, neck, others), malignancy (CNS, solid tumor outside the CNS, hematological), hematological conditions (polycythemia, thrombocythemia, anemia), mechanical (cranial trauma, jugular catheter occlusion, neurosurgery), CNS disorders (dural fistulae, venous anomaly, arteriovenous malformation), and other systemic disorders (cardiac insufficiency, hemoglobinopathy, hepatic insufficiency).

2.4. Outcomes

The primary outcome was VTE recurrence at any venous site. VTE

Table 1
Characteristics of the patients at the first event of cerebral venous thrombosis.

Characteristics	
Age at diagnosis of first event, median (IQR)	30.8 (24.7–40.9)
Female sex, n (%)	175 (86.2)
Site of CVT (Site of thrombosis), n (%)	
Superior sagittal sinus	73 (36.0)
Inferior sagittal sinus	3 (1.5)
Sagittal sinus without precise location	39 (19.2)
Transverse sinus	93 (45.8)
Straight sinus	16 (7.9)
Cavernous sinus	4 (2.0)
Cortical veins	7 (3.4)
Jugular vein	17 (8.4)
Sigmoid sinus	60 (29.6)
Combined location	86 (42.4)
Risk factor for first event of CVT, n (%)	
Idiopathic	54 (26.6)
Provoked	149 (73.4)
With one risk factor	137 (67.5)
With multiple risk factors	12 (5.9)
Description of the risk factor, n (%)	
Oral contraceptive*	106 (65.4)
Hormone replacement therapy*	4 (2.5)
Pregnancy*	2 (1.2)
Puerperium*	13 (8.0)
Otitis	1 (0.5)
Sinusitis	8 (3.9)
Other infections	8 (3.9)
Miscellaneous risk factors	20 (10)
Hereditary thrombophilia	
Factor V Leiden, n (%)	
No	180 (88.7)
Yes	12 (5.9)
Prothrombin G20210A mutation, n (%)	
No	175 (86.2)
Yes	18 (8.9)
Anticoagulant therapy, n (%)	
VKA	185 (91.1)
None	18 (8.9)
Duration of treatment with VKA in months, median (IQR)	9.9 (6.9–14.4)
Follow-up time in months, median (IQR)	36 (14.5–67.8)

* Percentage calculated considering 162 females of reproductive age (between 18 and 50 years). Some patients exhibited more than one site affected by CVT and more than one risk factor. Some data are missing for some variables. VKA, vitamin K antagonist; IQR, interquartile range; CVT, cerebral venous thrombosis.

events were defined as those confirmed by at least one of the following objective methods: angiography, MRI, CT, scintigraphy, venous duplex ultrasound, venography, arteriography, and Doppler ultrasound. At the end of anticoagulation for a CVT event, patients were reassessed by objective method which was used as a baseline after treatment. Therefore, a recurrent event was defined when patients had symptoms of VTE which were confirmed by identification of a new filling defect by a new objective method.

2.5. Statistical analysis

Dichotomic variables were expressed as number and percentage, and continuous variables were expressed as median and interquartile range (IQR), when data were non-normally distributed by the Kolmogorov-Smirnov test. Crude incidence rates with 95% confidence intervals (CIs) of recurrent thrombotic events were calculated as the number of events that occurred during the cumulative observation period. Incidences and 95% CIs were calculated assuming Poisson distribution. The ratio between incidence rates and their 95% CI was calculated to determine the relative risk of recurrence between the subgroups. Univariate analysis was performed to identify variables associated with VTE recurrence, using chi-square test and Cox regression analysis for each variable separately (age at the time of diagnosis of the first event, sex, factor V Leiden, prothrombin G20210A mutation, risk factors associated with the first event, and duration of anticoagulation). Multivariate Cox regression analysis was performed to assess the association between risk factors and the outcome. The model was adjusted with significant variables in the univariate analysis which were the variables known to be important as potential risk factors for VTE. Kaplan-Meier was used for survival analysis and cumulative incidence of recurrent events over time after a first CVT.

Sensitivity analyses were performed for three models: (i) model A, excluded patients who discontinued anticoagulation therapy after June 30, 2014 and thus did not have a minimum follow-up of 6 months. Bias may arise when follow-up time does not end on a specified date, because subjects may have a reason not to return to the clinic nor answer a telephone call. Therefore, we performed a second sensitivity analysis (ii) in which follow-up time started when vitamin K antagonists were withdrawn and ended at time of recurrence or January 15, 2015, whichever occurred first (model B) and (iii) model C, which combined models A and B.

All analyses were performed using the SPSS software v21.0 (IBM Corp., Armonk, United States).

3. Results

3.1. Patients' characteristics

A total of 245 patients with diagnosis of a first CVT were selected. Forty-two (17%) patients were excluded due to reasons shown in Fig. 1. Therefore, 203 patients were enrolled. Clinical and demographic characteristics of the cohort is detailed in Table 1.

Median age at diagnosis of first event was 30.8 (IQR, 24.7–40.9) years. A total of 175 (86.2%) patients were female, of whom 162 (92.6%) were considered as potentially fertile (age 18–50 years). A total of 106/175 (65.4%) women developed CVT while using oral contraceptives and 13 (8.0%) during puerperium. CVT was unprovoked in 54 (26.6%) patients. Ninety-three patients (45.8%) had CVT in the transverse sinus, 73 (36.0%) in the superior sagittal sinus, and 60 (29.6%) in the sigmoid sinus. CVT was diagnosed in multiple sinuses in 86 (42.4%) patients. There was one associated risk factor for VTE in 137 (67.5%) patients and multiple risk factors in 12 (5.9%) patients. Heterozygous prothrombin G20210A mutation was present in 18 (8.9%) patients and heterozygous factor V Leiden mutation was identified in 12 (5.9%) patients. A total of 185 (91.1%) patients were treated with VKA after CVT diagnosis. The median duration of the anticoagulant therapy was 9.9 (IQR, 6.9–14.4) months. The median cohort follow-up was 36 (IQR, 14.5–67.8) months (Table 1).

3.2. Outcomes

A total of 14/203 (6.9%) patients were lost to follow-up leaving 189 patients for the final analysis. Of these, 13 (6.8%) patients developed a recurrent VTE, which were classified as CVT in two (1.1%) patients, pulmonary embolism (PE) in three (1.6%), and deep vein thrombosis (DVT) of the lower limbs in eight (4.2%). Among the 13 patients who recurred, three (23%) developed a recurrent event during the first year.

During a follow-up of 805.4 patient-years, the overall incidence rate was 1.6 (95% CI, 0.8–2.8) cases per 100 patients/year, when all types of recurrent VTEs were taken into account. The recurrence rate of CVT and other types of VTE was 0.2 (95% CI, 0.0–0.9) and 1.4 (95% CI, 0.7–2.4) cases per 100 patients/year, respectively. PE and DVT of the lower limbs accounted for 0.4 (95% CI, 0.1–1.1) and 1.0 (95% CI, 0.4–2.0) cases per 100 patients/year, respectively. Table 2 shows the recurrence rate after the first CVT event, which was stratified according to the site of recurrence, sex, prothrombin G20210A mutation, factor V Leiden mutation, and risk factors associated with the first CVT event (i.e., provoked and unprovoked first CVT event).

VTE recurrence rate was higher in males (4.6; 95% CI, 1.2–11.7

Table 2
Recurrence of venous thromboembolism after a first event of cerebral venous thrombosis.

	Recurrence (n = 13)	Follow-up (patients/year)	IR (95% CI) per 100 patients/year	IRR (95% CI)	IRR (95% CI)*	IRR (95% CI)†	IRR (95% CI)‡
Type of recurrence							
CVT	2	805.4	0.2 (0.0–0.9)	Reference	Reference	Reference	Reference
VTE (PE, DVTLL)	11	805.4	1.4 (0.7–2.4)	5.5 (1.2–24.8)	5.5 (1.2–24.8)	5.5 (1.2–24.8)	5.5 (1.2–24.8)
PE	3§	805.4	0.4 (0.1–1.1)	1.5 (0.3–9.0)	1.5 (0.3–9.0)	1.5 (0.3–9.0)	1.5 (0.3–9.0)
DVTLL	8	805.4	1.0 (0.4–2.0)	4.0 (0.8–18.8)	4.0 (0.8–18.8)	4.0 (0.8–18.8)	4.0 (0.8–18.8)
Type of event							
Provoked	10	610.7	1.6 (0.8–3.0)	Reference	Reference	Reference	Reference
Unprovoked	3	194.6	1.5 (0.3–4.5)	0.9 (0.3–3.4)	0.9 (0.3–3.4)	0.9 (0.2–3.2)	0.9 (0.2–3.2)
Sex							
Female	9	717.6	1.2 (0.6–2.4)	Reference	Reference	Reference	Reference
Male	4	87.7	4.6 (1.2–11.7)	3,6 (1.1–11.8)	3.6 (1.1–11.8)	3.6 (1.1–11.8)	3.5 (1.1–11.5)
Thrombophilia							
None	8	663.6	1.2 (0.5–2.4)	Reference	Reference	Reference	Reference
Heterozygous factor V Leiden	2	21.8	9.2 (1.1–33.1)	7.6 (1.6–35.8)	7.6 (1.6–35.8)	8.8 (1.9–41.4)	8.8 (1.9–41.4)
Heterozygous prothrombin mutation (G20210A)	4	76.4	5.2 (1.4–13.4)	4.3(1.3–14.4)	4.3 (1.3–14.4)	4.3 (1.3–14.4)	4.4 (1.3–14,4)

IR, incidence rate; IRR, incidence rate ratio; PE, pulmonary embolism; CVT, cerebral venous thrombosis; DVTLL, deep vein thrombosis of the lower limbs; n/a, not assessed.

§ A patient had an episode of PE and concomitant DVTLL.

* Model A: Excluding patients whose oral anticoagulant therapy was not discontinued before June 30, 2014.

† Mode B: Excluding patients whose last contact occurred before January 15, 2015.

‡ Model C: Those fulfilling both models A and B.

cases per 100 patients/year) when compared with females (1.2; 95% CI, 0.6–2.4) cases per 100 patients/year (Table 2 and Fig. 2). The recurrence rate in patients with a provoked event was 1.6 (95% CI, 0.8–3.0) cases per 100 patients/year and that of patients with an unprovoked event was 1.5 (95% CI, 0.3–4.5) cases per 100 patients/year. There was no difference in the risk of recurrence according to the nature of the first event (whether provoked or unprovoked).

In patients without prothrombin G20210A and factor V Leiden mutations (n = 8), the recurrence rate was 1.2 (95% CI, 0.5–2.4) cases per 100 patients/year. The recurrence rate was 5.2 (95% CI, 1.4–13.4) cases per 100 patients/year in patients with heterozygous prothrombin G20210A mutation and 9.2 (95% CI, 1.1–33.1) cases per 100 patients/year in those with heterozygous factor V Leiden mutation. The characteristics of the patients with recurrent VTE are described in the Supplementary Table.

When we analyzed patients with recurrent VTE, we noted that 9/13 (69.2%) events occurred in females. Of these, 66.7% had a provoked VTE as the first event. A total of 4 (30.8%) males relapsed, of whom one had a provoked VTE as the first event (Supplementary table).

Univariate analysis revealed that male sex (hazard ratio [HR], 3.6; 95% CI, 1.1–11.5), presence of heterozygous factor V Leiden mutation (HR, 5.2; 95% CI, 1.1–25.0), heterozygous prothrombin G20210A mutation (HR, 4.5; 95% CI, 1.4–14.5), and age at diagnosis of the first event (HR, 1.1; 95% CI, 1.0–1.1) were associated with recurrence (Table 3). In the final Cox regression model, male sex (HR, 4.2; 95% CI, 1.2–14.1) and the presence of heterozygous factor V Leiden mutation (HR, 6.8; 95% CI, 1.3–34.2) were shown to be associated with risk of recurrent VTE after a first CVT event (Table 3).

For the sensitivity analyses, we excluded patients whose oral anticoagulant therapy was not discontinued before June 30, 2014 (model A), those whose last contact occurred before January 15, 2015 (model B), and those fulfilling both model A and B criteria (model C). The recurrence rates were not different in models A, B, nor C (Table 2).

4. Discussion

We followed up a cohort of about 200 patients for a median of 3 years and found that 13 (6.9%) had a recurrent VTE after a first CVT event. Male sex and factor V Leiden mutation were the only factors associated with a significant higher risk of recurrent VTE after a first CVT in a multivariate analysis. Recurrence of VTE after a first CVT event was low.

In this study, VTE recurrence rate was 1.6, 1.4, and 0.2 cases per 100 patients/year for all types of VTE, DVT/PE and CVT, respectively. This result corroborates with the findings of other studies [2,7,8,11]. Dentali et al. [7], in an international, multicenter and retrospective study followed 706 patients for a median period of 3.3 years after a first CVT. The overall recurrence rate was 3.5 cases per 100 patients/year after discontinuing anticoagulant therapy [7]. In another cohort study with 145 patients with CVT who were followed for a median period of 6 years, Martinelli et al. [2] showed that after discontinuing anticoagulation, 3% had recurrent CVT and 7% had DVT/PE; the overall recurrence rate was 0.5 cases per 100 patients/year for CVT and 2.0 cases per 100 patients/year for all VTE. In the ISCVT study, an observational, multicenter and prospective study, 624 patients from 21 countries were followed for a median period of 16 months after CVT. CVT recurrence rate was 1.5 cases per 100 patients/year and the incidence at other sites was 4.1 cases per 100 patients/year [8,11,12]. The differences in the incidence rates between these studies are small, but they are likely influenced by the differences in the follow-up time and sociodemographic characteristics of participants. In the ISCVT study, the follow-up period started at diagnosis, continued during the anticoagulant therapy, and after its discontinuation; this may have affected the incidence rates because the follow-up period included a period when patients were on anticoagulant therapy and were potentially protected against the occurrence of new events [11]. In our study, 23% of recurrences occurred during the first year.

In our study, a higher recurrence rate was observed in males compared with females. This is corroborated by other 2 studies [2,11]. Martinelli et al. [2] reported a higher CVT recurrence rate in males (5.0 events per 100 patients/year) than in females (0.7 events per 100 patients/year). Miranda et al. [8] observed that male sex was a risk factor for VTE recurrence after CVT, with HR of 2.6.

In our study, the recurrence rate was also higher in patients with heterozygous factor V Leiden mutation and prothrombin G20210A mutation compared with patients without these mutations. However, after a multivariate analysis, only heterozygous factor V Leiden mutation remained independently associated with recurrence. This finding is not in line with previous studies [2,7,8]. Indeed, each of these 3 studies found different factors associated with recurrence of VTE after CVT. In

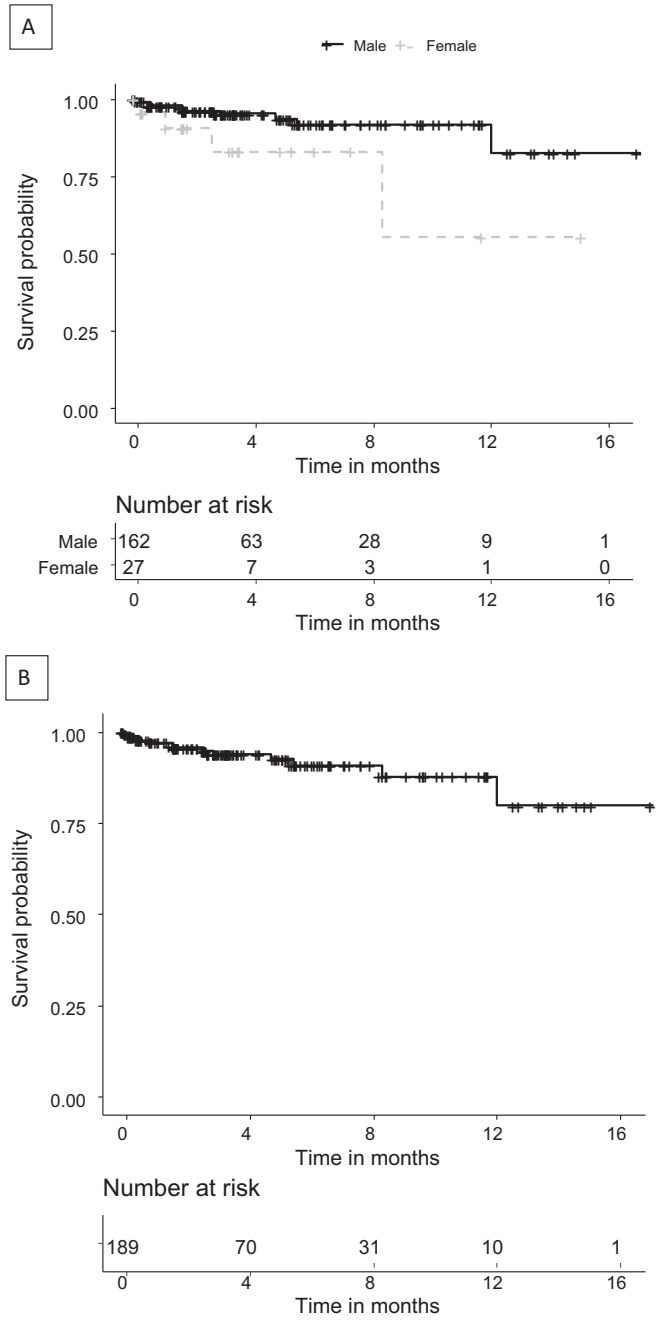

Fig. 2. Kaplan-Meier showing the survival analysis for the entire cohort (B) and the cohort stratified by sex (A).

the study by Miranda et al. only male gender and polycythemia/thrombocythemia were significantly associated with a higher risk of VTE [8]. Martinelli et al. found association for male gender and severe thrombophilia [2] and Dentali et al. reported association with personal history of previous VTE [7]. Therefore, none of these studies confirmed the risk factors found by others. This difference across the studies might be related to different selection criteria of patients, relatively small sample size of most studies and demographic variability. Recently, Lauw et al. [13] conducted a meta-analysis with inconclusive results with regard to the association between the presence of thrombophilia and recurrent CVT and other types of VTE.

In our study, about half of the recurrences were associated with at least one risk factor for VTE. Interestingly, among the four patients with heterozygous prothrombin G20210A and factor V Leiden mutations who recurred, three exhibited associated acquired risk factors (pregnancy, puerperium, and hospitalization for clinical condition). Unfortunately, we could not recover information about use of thromboprophylaxis during these risk situations for VTE. Nonetheless, the association of prothrombotic mutations and acquired risk factor for VTE might be of relevance in the recurrence of VTE after a first CVT. However, due to the rarity of CVT, further studies with a large number of patients are needed to investigate this.

Table 3
Univariate and multivariate analysis of risk factors for recurrence of venous thromboembolism after a first event of cerebral venous thrombosis.

Risk factors	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Sex	3.6	1.1–11.6	4.2	1.3–14.1
Heterozygous factor V Leiden	5.2	1.1–25.0	6.8	1.3–34.2
Heterozygous prothrombin mutation	4.5	1.4–14.5		
Risk factors related to the first CVT event	1.1	0.3–3.9		
Age at diagnosis of the first CVT event	1.1	1.0–1.1		
Duration of anticoagulant therapy (in years)	0.6	0.2–2.1		

CI, confidence interval; CVT, cerebral venous thrombosis; HR, hazard ratio; VTE, venous thromboembolism.

In this study, the nature of the first CVT event, whether provoked or unprovoked, was not associated with recurrence rate. This finding suggests a difference in the nature of CVT and VTE at other sites, where it is known that patients with unprovoked DVT and PE are more likely to experience recurrence [2].

One of the strengths of this study was to investigate VTE recurrence rate of CVT in a South-American population. Since ethnicity appears to influence the risk for VTE, and the prevalence of prothrombotic mutations varies in different populations [9,10], investigating VTE in populations other than Caucasian is relevant. This study has some limitations. Firstly, the patients were selected from those who visited the thrombophilia and anticoagulation clinics, which could restrict the generalization of our results. However, other studies have also reported the same limitation [2,7]. Secondly, the sample size was not previously calculated as CVT is a rare condition. However, sample size was similar or even larger than that of most studies which assessed CVT recurrence [2,14,15]. Thirdly, objective methods to diagnose CVT and its recurrence were performed in the participating centers and were not confirmed by the coordinating center. However, all centers followed the guidelines for CVT recurrence using objective methods. Because this fact may result in non-differential misclassification, there could be a tendency to reduce the estimated risk toward the null value. Fourthly, 14 patients (6.9%) were lost to follow-up. This could have affected the estimation of the recurrence rate. Fifthly, other types of thrombophilia such as antithrombin deficiency, protein C and S deficiency, and presence of antiphospholipid antibodies were not analyzed. However, when these conditions are identified in patients with a first idiopathic CVT event, indefinite anticoagulation are likely to be indicated and will therefore decrease recurrence rates [2].

In conclusion, male sex and the heterozygous factor V Leiden mutation were associated with a significant higher risk of recurrent VTE after a first CVT in a multivariate analysis. VTE recurrence after a first CVT was low.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.008.

Addendum

G. S. Pires, D. D. Ribeiro, and S. M. Rezende designed the study. G.

S. Pires, J. A.Q. Oliveira, L. C. Freitas, R. Vaez, J. M. Annichino-Bizzacchi, and V. M. Morelli collected the data. G. S. Pires, D. D. Ribeiro, and S. M. Rezende analyzed the data. G. S. Pires, D. D. Ribeiro, and S. M. Rezende drafted the manuscript. G. S. Pires, D. D. Ribeiro, J. A. Q. Oliveira, L. C. Freitas, R. Vaez, J. M. Annichino-Bizzacchi, V. M. Morelli, and S. M. Rezende reviewed the final manuscript.

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Competing interests

The authors state that they have no competing conflicts of interest.

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