Journal of Hematology & Thromboembolic Diseases

Kostal et al., J Hematol Thrombo Dis 2017, 5:6
DOI: 10.4172/2329-8790.1000278

Research Article Open Access

Risk and Prognostic Factors in Cerebral Venous Thrombosis

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Received date: October 27, 2017; **Accepted date:** November 14, 2017; **Published date:** November 17, 2017

Abstract

Objective and design: Cerebral venous thrombosis (CVT) differs from deep venous thrombosis (DVT) in prognosis, risk factors and treatment. We analyzed data gathered in our prospective CVT single-center registry in search of risk and prognostic factors. Data from 73 patients were available.

Results: JAK2 mutation (11%) and Leiden mutation of factor V (11%) were the most common among genetic risk factors. The most common acquired risk factor was the use of combined hormonal contraception (COC) or hormonal replacement therapy (HRT) in 64% of female patients. No specific cause was found in 22% of cases. Complete recanalization was present in 44% of cases, more often in female than in male (p=0.0287) and in younger patients (p=0.045). We found final mRS score one and higher in 29% of patients. These patients did not use COC/HRT (p=0.021) or did not achieve complete recanalization (p=0.0058). Patients with higher mRS score tend to be older (p=0.081).

Conclusions: COC/HRT use and complete recanalization can be considered when adjusting the length of anticoagulation therapy. JAK2 mutation should be screened in all patients with CVT.

Keywords: Contraception; Cerebral venous thrombosis; Thrombosis; Risk factors; Anticoagulation; Recanalization

Introduction

Before the era of hormonal contraception, cerebral venous thrombosis (CVT) used to be a rare and often fatal cause of stroke [1]. Two major discoveries changed the course of the disease in the 20th century. New imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) allow early diagnosis and combined hormonal contraception or hormonal replacement therapy changed the major risk factors [2,3]. Introducing heparins and warfarin later in the treatment of CVT over time has transformed life-threatening type of stroke into a disease with a mortality of less than 5% [4,5]. Although COC is the most common risk factor in women the search for other thrombophilic risk factors is still ongoing. We conducted a prospective study focused on well-known genetic and acquired thrombophilia (protein C and S deficiency, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation and factor V Leiden) and focused on the presence of myeloproliferative disease (overt or non-overt) by screening for JAK2 mutation.

Patients and Methods

We conducted analysis of data collected prospectively in our CVT registry. All consecutive patients with confirmed CVT treated at the University Hospital in Hradec Kralove between 2006 and 2015 who had a first ever non septic CVT diagnosed by MR-venogram (MRV) were included. Patients were treated acutely with low molecular weight heparin or thrombolysis followed by oral anticoagulation for 3-12 months depending on the type of thrombophilia, clinical result and recanalization at 3 months. Patients diagnosed with a specific clotting abnormality are considered to have a high risk of recurrence and received long-term anticoagulation. Patient data, including demographics, medical history, CVT onset time, in-hospital mortality and ambulatory status at discharge were registered in each case. We also investigated specific risk factors for CVT including recent use of hormonal contraceptives (defined as routine use at the time of diagnosis), history of abortions or miscarriages, pregnancy or post-partum, personal history of thrombophilia or antiphospholipid syndrome. At our institution, testing for prothrombotic conditions includes protein C, protein S and antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation and factor V Leiden and JAK2 and is performed immediately before starting anticoagulation or is completed during the follow-up period. Clinical presentation was categorized according to the major clinical syndromes that led to emergency department consultation: intracranial hypertension, seizures, motor deficit and others. The modified Rankin scale (mRS) was assessed at the time of the last follow-up (one year after the thrombosis) [6]. For statistical purposes, we classified patients as having no sequels at all (mRS of 0) or any sequels (mRS 1 to 6).

Statistical Analysis

We used descriptive statistics for demographics, risk factors and recanalization rate. In the primary analysis, we compared demographics, clinical manifestations, etiology and outcome between women and men. In the secondary analysis, we compared the influence of selected risk factors on the patient outcome. Categorical data were analyzed with the chi2 test or with the Fisher exact test for 2 × 2

contingency table because continuous data were not normally distributed, we used the Mann-Whitney test. The statistical analyses were performed with SigmaPlot for Windows, version 11.0. (Systat Software)

Results

We enrolled 73 patients with CVT out of the 73 patients, 53 were women (73%). The men were slightly older (mean age 40 years) than the women (mean age 35 years) with no statistical significance (p=0.443). The women have a shorter time from onset of symptoms to diagnosis than the men (median 7 days *vs.* 10 days, p=0.706). Risk factors for CVT are shown (Table 1).

Thrombophilia	Percentage
factor V Leiden	11% (8/71)
prothrombin G20210A	10% (7/72)
JAK2 mutation	12% (8/63)
Antiphospholipid syndrome	3% (2/69)
Hyperhomocysteinemia	4% (3/67)
Malignancy	5% (4/73)
Protein C deficiency	0% (0/67)
Protein S deficiency	1% (1/68
Antithrombin deficit	0% (0/69)
COC/HRT	51% (37/73) (70% of women)
Idiopathic CVT	22% (16/73)

Table 1: Occurrence of thrombophilic risk factors for CVT in 73 patients at the time of diagnosis, the number of positive patients among those examined is in brackets.

Major risk factors for women are COC or HRT (37 cases, 70%). Except COC/HRT, any other thrombophilia was found in 8 men (40%) and in 15 women (28%) (p=0.401). One patient died for a reason unrelated to the CVT (pulmonary cancer, mRS 6). 52 patients (71%) had mRS score 0.17, patients (23%) had mRS1, 2 patients had mRS2 and one had mRS3. In the COC/HRT group, mRS score was 1 and more in 16% while mRS score was 1 and more in 42% (p=0.021) in the non-user group. When the same analysis was done only for women, COC/HRT users had mRS 1 and more in 16% of cases while in non-users mRS was 1 and more in 44% of cases (p=0.043) (Table 2).

Factor	P
sex	0.248
COC/HRT-all	0.021
COC/HRT women only	0.043
recanalization	0.0058
Other thrombophilia	1
Age	0.081
Time to diagnosis	0.9
mRS at presentation	0.259

Table 2: Influence of risk factor on final mRS outcome score. mRS score is considered as excellent when it equals zero.

There was a non-significant difference in higher mRS (more than 0) according to gender men 40% *vs.* women 25% (p=0.248) (Table 3).

Parameters	All	Male (20pts.)	Female (53 pts.)	P
Age (mean)	36 years	40 years	35 years	0.443
Time to diagnosis (median)	7 days	10 days	7 days	0.706
Thrombophilia (COC/HRT excluded)	34%	28%	40%	0.401
mRS>0	29%	40%	25%	0.248
Complete recanalization	42%	21%	52%	0.0287

Table 3: Gender distribution of factors.

We observed complete recanalization in 44% of patients, partial in 40% of patients and no recanalization in 16% of patients. Complete recanalization was more often achieved in women (52%) than in men (21%) (p=0.0287) and was more common in patients with excellent prognosis (mRS=0) (p=0.0058) or with COC/HRT use (p=0.00131). Patients with complete recanalization were younger (median 31 *vs.* 35.5 years, p=0.045).

Discussion

We focused on the risk factors and possible prognosis-bearing factors in CVT. Cerebral venous thrombosis shares some of the same risk factors as DVT. However, there are some important differences compared to deep venous thrombosis. Veins lack a muscular layer, valves, muscle pump and are uncompressible. The direction of blood flow is guided by gravity and intracerebral pressure. That may be the reason for the different risk factors in comparison to DVT. For example, JAK2 mutation is rarely the cause of DVT (less than 1 %) [7,8]. On the other hand, JAK2 mutation is often found in thrombosis of unusual sites like Budd-Chiary syndrome, splanchnic thrombosis or CVT [9]. We found JAK2 mutation and Leiden mutation of f.V as the most common genetic thrombophilia. This finding is similar to other published data [10,11]. The clinical significance of JAK2 mutation and its consequences for the patients are however much higher for JAK2 than for other mutations. In our set of patients 7 out of 8 patients developed/or already had myeloproliferative disease which was the indication for cytoreductive treatment. We therefore support routine testing for JAK2 in the case of CVT (rather than other mutations).

We had slightly more patients diagnosed with Leiden mutation than with prothrombin mutation. This is in contrast to the large multicenter study published by Dentali in which we shared part of our data [11]. This might be due to the uneven geographic distribution of prothrombin mutation in Europe (which is more common in the south) [12]. The presence of any thrombophilia apart from COC had no strong prognostic relevance for the outcome of the patient. This might be influenced by the smaller size of our set of patients. Nevertheless, strong prognostic factors should emerge.

Combined hormonal contraception or hormonal replacement therapy is known as a weak, but the most common, risk factor for thrombosis [13]. We confirm that women taking this medication have a better prognosis than others as published by Coutinho from the ISCVT study [14]. This might be due to the fact that COC users are younger otherwise healthy and COC/HRT is fully stoppable at the time of diagnosis. Age seems to be a weak risk factor for CVT. In our analysis, it did not reach statistical significance. We assume that this is only because of the small sample test.

For evaluation of patient's outcome we used mRS scoring system. Fortunately patients with CVT have generally good prognosis with mRS ranging between 0 and 1. The most commonly used cut-off value for mRS score is 2, but there were only 4 patients having such high mRS score making statistical analysis impossible. Sample size is one of the most important limitations of this registry. CVTs are still rare type of stroke with annual incidence about 8 cases in our region. We therefore simplified outcome only to 2 major groups: without having any long-term sequels (at 1 year follow up visit-mRS=0) or with mRS 1 and more.

Recanalization and D-dimers measured after discontinuation of anticoagulant therapy in DVT have a prognostic value for recurrence [15,16]. Not much is known about recurrence in CVT. Dentali found only personal history, recent head trauma and cancer to be risk factors for recurrence. Recurrence occurs in only about 10% of patients [11]. This makes such an analysis in our list impossible. On the other hand in Dentali's work anticoagulation above 1 year did not reduce the recurrence rate. But is prolonged anticoagulation beneficial for prognosis (if not for recurrence) of patients. We confirmed that patients with full recanalization have a better functional outcome. Similar data were published recently by Arouz et al [17]. These patients are also younger; more often female and taking contraceptive pills (if female). Recanalization occurs mainly in the first 3-4 month after thrombosis but can happen within the first year from diagnosis [17,18]. It might be important to extend anticoagulation treatment (usually with LMWH or warfarin) till 1 year in cases where only partial or none recanalization was observed [11,19].

Conclusion

In our set of CVT patients, JAK2 mutation and myeloproliferation were common risk factors. We have furthermore confirmed COC and recanalization as positive prognostic factors in CVT patients. Duration of anticoagulation therapy could be guided by presence of recanalization. We support testing for JAK2 mutation in all cases of CVT.

Funding

This study was supported by program PROGRES Q40/08

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