Venous thrombosis and relapses in patients with Behçet's disease. Descriptive analysis from Spanish network of Behçet's disease (REGEB cohort)

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ABSTRACT

Objective. *To describe the characteristics of patients with Behçet's disease (BD) who presented with venous thrombosis. In addition, we identified the factors associated with this venous involvement and those related with recurrent venous thrombosis.*

Methods. *Up to January 2015, 544 BD patients from 20 Spanish hospitals had been included in the REGEB* (REGistro de la Enfermedad de Behçet *as Spanish nomenclature). We selected those patients who presented venous thrombosis. Descriptive analysis was performed and factors related with venous thrombosis were identified.*

Results. *Overall, 99 (18.2%) BD patients had vascular thrombosis, 91 (16.7%) of them (16.7%) involving venous vessels and 18 (19.7%) suffered from venous thrombotic relapse. Lower limbs were the most common location of deep venous thrombosis present in up to 60% of patients. In 12 (13.2%) patients, venous thrombosis affected two vascular territories simultaneously and in 6 (6.6%) the venous and arterial involvement coincided in time. Overall, at the diagnosis of venous thrombosis, 97.6% of patients presented concomitantly other clinical symptoms attributable to BD. In logistic regression multivariate analysis factors associated to venous thrombosis were male sex (Odds ratio [OR] 4.3, 95% confidence interval [CI] 2.5-7.7), erythema nodosum (OR 2.4, 95%CI 1.4-4.1), fever (OR 2.0, 95%CI 1.1-3.8), and central nervous system (CNS) involvement (OR 2.5, 95%CI 1.3-4.8). Considering relapses, CNS involvement was an independent risk factor according logistic regression. However, Cox multivariate analysis did not confirm this finding.*

Conclusion. *We identified factors related with venous involvement in patients included in the REGEB cohort.*

Introduction

Thrombosis tendency is a hallmark of Behçet's disease (BD); it is mainly seen among men and venous involvement is much more frequent than arterial, with a prevalence ranging from 5% to 40% (1). Of note, the relapse rate of venous thrombosis is around 40% despite treatment. Up to 70% of venous thrombosis occur in lower extremity although vena cava thrombosis, Budd-Chiari syndrome, and cerebral sinus thrombosis, do also occur (2).

Actually, the current recommendations of treatment of the venous thrombosis include the use of corticosteroids and immunosuppressive agents (3). In the last systematic literature review (4) anticoagulation did not provide any additional benefit.

The aim of the present study was to describe the main characteristic of a large cohort of patients with BD who presented with venous thrombosis. In addition, we tried to identify the factors associated with this venous involvement and those related with recurrent venous thrombosis.

Patients and methods

The Spanish Registry of Behçet's Disease (SRBD) or REGEB (*REGistro de la Enfermedad de Behçet* as Spanish nomenclature) Project Group is the first nationwide cross-registry created by the Spanish Society Internal Medicine in 2009 (5). We considered BD diagnosis when patients fulfilled criteria

of International Study Group (ISG) (6). Demographic and clinical data defined previously encompassing more than 70 variables were collected retrospectively (5). The Ethics Committee of each participating centre approved the study and written informed consent was obtained from all patients.

Venous thrombosis and relapses were diagnosed with clinical findings and confirmed if necessary, by objective methods using imaging techniques. Relapse was defined as a new occurrence of venous thrombosis at another site or as an extension of the previous thrombosis. Other clinical manifestations of BD, treatment of first venous thrombosis and relapses were recorded from patient records. For each patient, the diagnosis of venous thrombosis, treatment, and follow-up were done according to the criteria of the attending physician.

Statistical analysis

Categorical data are summarised as percentages and continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]) depending on the normality of the distributions. To analyse the characteristics of patients with venous thrombosis and factors related with venous relapses, significant differences or associations were analysed using the χ^2 *test* or Fisher's exact tests. Associations of quantitative data were analysed with Student's *t*-test and with the non-parametric Mann-Whitney U-test. A two-tailed value of $p<0.05$ was taken to indicate statistical significance. When independent variables appeared to have statistical significance in the univariate analysis ($p<0.05$), they were included in a multivariate logistic regression analysis using a backward stepwise method. The odds ratios (OR) and their 95% confidence interval (95% CI) obtained in the adjusted regression analysis were calculated. Associations between variables and time to relapse were evaluated using a cause-specific Cox random-effects model. Statistical analysis was performed using the SPSS program (IBM Corp. 2010, Armonk, NY, SPSS Statistics 19.0).

Results

By January 2015, REGEB included 544 patients, 284 (52.2%) of them were female and the mean ± SD age of onset disease was 28.8±12.3 years. The median delay in diagnosis was 24 (3-72) months. The median follow-up was 131 (56-236) months.

Characteristics of patients with venous thrombosis

During the follow-up, 99 (18.2%) patients had thrombosis, 91 (16.7%) of them involving venous vessels, with a total of 114 thrombotic events. Of note, in 35 (6.4%) of them appeared as a presenting manifestation of the disease.

The main demographic and clinical features of the 91 patients with venous thrombosis are summarised in Table I. The location of single and multiple venous involvement and the BD clinical characteristics present at time of venous thrombosis are described in Table II. Considering the first thrombotic event, in 12 (13.2%) patients venous thrombosis affected two vascular territories simultaneously (Table II) and in 6 (6.6%) the venous and arterial involvement coincided in time. Overall, at the diagnosis of venous thrombosis 82 (97.6%) patients presented concomitantly other clinical symptoms attributable to BD (Table II).

Compared to patients without venous involvement, those with venous thrombosis were more frequently male (70.3% versus 43.3%; $p<0.001$) and had more fever (32.1% versus 18.7%; $p=0.01$), erythema nodosum (50.6% versus 35.5%; $p=0.01$), and central nervous system (CNS) involvement (27.0% versus 11.1%; $p<0.001$) especially in form of *pseudotumour cerebri* (12.2% versus 1.2%; $p<0.001$) (Table I). In a logistic regression multivariate analysis, factors associated to venous thrombosis were male sex (OR 4.3, 95%CI 2.5-7.7), erythema nodosum (OR 2.4, 95%CI 1.4-4.1), fever (OR 2.0 95%CI 1.1-3.8) and CNS involvement (OR 2.5, 95%CI 1.3-4.8).

The treatment of the first thrombotic episode (n=84) includes anticoagulation (AC) in 63 (82.9%) patients, glucocorticoids (GC) in 43 (51.2%), immunosuppressive (ISS) agents in 23 (27.4%), and infliximab in 2/84 (2.4%), respectively.

Characteristics of patients with recurrent venous thrombosis

From the initial 91 BD patients with venous thrombosis, we excluded 7 (7.7%) patients due to the lack of relevant data. Finally, we analysed 84 patients of whom 18 (19.7%) presented a second episode of thrombosis and 5 (5.5%) of them a third episode. We analysed all these 23 recurrent episodes of thrombosis together. The median time between thromboses was 24 months (12-152).

Recurrent thrombosis included lower limbs thrombosis in 14 cases, vena cava in 4, cerebral veins in 4, and superficial thrombophlebitis, suprahepatic veins, and right ventricle thrombosis in one case each (one patient presented two venous locations simultaneously).

At the diagnosis of thrombosis relapse, concomitant clinical symptoms attributable to BD were detected in 20 (86.9%) patients and they included oral ulcers in 14 (60.9%), arthritis in 8 (34.8%), genital ulcers in 6 (26.1%), pseudofolliculitis in 3 (13%), erythema nodosum in 3 (13%), retinal vasculitis in 3 (13%), anterior uveitis in 3 (13%), posterior uveitis in 2 (8.7%), and aseptic meningitis in 2 (8.7%).

Univariate analysis showed significant association between thrombosis relapses and CNS involvement (61.1% versus 32.8%; $p=0.03$). The logistic regression confirmed this relationship (OR 4.3, 95%CI 1.3-14.2; $p=0.017$). However, Cox multivariate analysis did not identify this variable as independent risk factor of recurrent thrombosis.

Relapses were treated with the combination of AC plus GC plus ISS in 9 (39.1%) patients, with AC in 7 (30.4%), with AC plus GC in 4 (17.4%), with GC plus ISS in 2 (8.7%), and one patient received only GC. The low number of patients treated with only AC or ISS precluded comparative analysis to evaluate the role of these treatments in recurrent thrombotic events.

Discussion

In the present study, the rate of venous thrombosis was 16.7% and that

of thrombosis relapses 19.7%. Lower limbs were the most common location of deep venous thrombosis present in up to 60% of patients. At the diagnosis of venous thrombosis, almost all patients presented concomitantly other clinical symptoms attributable to BD. Finally, male sex, fever, erythema nodosum, and CNS involvement were identified as factors associated to venous thrombosis in BD.

Prevalence of venous thrombosis varies widely among different studies (2). Our results are in accordance to those from the same geographical area (7, 8). Conversely, series from Turkey (9) and China (10) presented higher prevalence of vascular involvement.

The prevalence of thrombosis relapses in our series was 19.7%. In a prospective study thrombosis relapses were described in about 20% during the first year and about 40% during the second year (11). In a recent retrospective study the cumulative risk of a recurrent vascular event was 23% at 2 years and 38.4% at 5 years (12).

Most of patients with venous thrombosis in the present series were diagnosed with concomitant clinical symptoms attributable to BD. In a recent series of 93 Chinese patients, active BD according to the BD Current Activity Form was documented in all of them during thrombosis onset (13).

Different studies consistently revealed the association of male gender with both vascular (venous and arterial) involvement and specifically venous involvement. A recent study confirmed the association of male gender with deep venous thromboses (RR 2.56). In the same study, a meta-analysis from a systematic literature review confirmed these results (RR 2.16) (14).

In a series of 500 BD patients, those with fever episodes were more likely to have vascular involvement (15). Considering CNS involvement and its association with thrombosis in BD, the results are contradictory. In some studies, the prevalence of CNS involvement was similar in patients with and without vascular involvement (10). On the other hand, applying factor analysis, CNS involvement was associated with deep venous thrombosis (16). In our cohort from REGEB, pseudotumour cerebri was associated with venous thrombosis. The main cause of intracranial hypertension is cerebral sinus venous thrombosis (17). However, in our study none of these patients presented with parenchymal CNS or cerebral venous involvement, ruling out the possibility of a causal association.

Table I. Comparison of demographic and clinical characteristics of patients with Behçet's disease according to the presence or absence of venous involvement.

	With venous thrombosis (n=91)	Without venous thrombosis (n=453)	*p*
Demographic characteristics			
Male sex	64 (70.3)	196 (43.3)	<0.001
Age at disease onset, mean ± SD (years)	27.3 ± 10.5	29.1 ± 12.7	NS
Time onset-diagnosis, median (IQR)(months)	21 (3-108)	24 (3-72)	NS
Follow-up, median (IQR), (months)	154 (209)	114 (171)	0.006
Ethnic origin:			
Caucasian	82 (90.1)	422 (93.2)	NS
Arabic	8 (8.8)	20 (4.4)	
African	1 (1.1)	6 (1.3)	
Others	0	5 (1.0)	
Cumulative BD clinical manifestations			
Oral ulcers	91 (100)	453 (100)	NS
Genital ulcers	66 (72.5)	286 (72.4)	NS
Fever	26 (32.1)	62 (18.7)	0.01
Skin involvement	77 (81.3)	340 (75.1)	NS
Pseudofolliculitis	51 (56.0)	184 (48.3)	NS
Erythema nodosum	43 (50.6)	129 (35.5)	0.01
Ocular involvement	44 (48.4)	203 (44.8)	NS
Retinal vasculitis	18 (19.8)	58 (12.8)	NS
Posterior uveitis	4 (4.4)	73 (16.1)	0.03
Anterior uveitis	37 (40.7)	138 (30.5)	NS
Arthritis	35 (38.5)	153 (40.7)	NS
Central nervous system involvement	24 (27.0)	50 (11.1)	<0.001
Aseptic meningitis	9 (10.8)	32 (9.2)	NS
Pseudotumour cerebri	10 (12.2)	4 (1.2)	<0.001
Arterial involvement	6 (6.6)	14 (3.1)	NS
Arterial aneurysm	2 (2.4)	2 (0.6)	NS
Peripheral nervous system involvement	3 (3.7)	9 (2.6)	NS
Gastrointestinal involvement	0	11 (2.4)	NS
HLA-B51 positive	27/84 (42.9))	11/56 (19.6)	NS
Death	2 (3.1)	3 (1.2)	NS

Categorical variables are presented as number (percentage) and continuous as mean and SD or median and IQR. The Bonferroni adjustment was used due to the multiple testing
BD: Behçet's disease; IQR: interquartilic range, SD: standard deviation.

Conclusion

The main strengths of the present study include the large number of patients with BD and venous thrombosis derived from the Spanish geographical location. However, our study has several limitations, including its retrospective design. In addition, registry studies derived from reference hospitals tended to collect patients with more severe disease. Some of the statistical significant differences associated to venous involvement could be due to this fact and to the number of patients analysed. Finally, discrepancies between published studies could be secondary to genetic background and differences in study designs or variable definitions. In spite of these limitations, our study represents a real picture of Spanish patients with BD and venous involvement.

Appendix

Members of the SRBD Project

The members of the SRBD Project Group or REGEB (REGistro de la Enfermedad de Behçet) who contributed to this study are as follows:

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Table II. Clinical characteristics of BD patients with venous involvement.

	n (%)
Characteristics of venous involvement[a]	
Superficial venous thrombosis	7 (7.7)
Deep venous thrombosis	87 (95.6)
Location of venous thrombosis	
Lower limbs	53 (58.2)
Pulmonary embolism	10 (10.9)
Superior/inferior cava	9 (9.9)
Cerebral veins	8 (8.8)
Retinal vein	4 (4.4)
Suprahepatic vein	2 (2.2)
Right ventricle	1 (1.1)
Single vein thrombosis	79 (86.8)
Multiple vein thrombosis	12 (13.2)
Lower limbs and pulmonary embolism	6 (6.6)
Bilateral lower limbs	2 (2.2)
Lower limbs and cerebral veins	1 (1.1)
Subclavian vein and pulmonary embolism	1 (1.1)
Jugular and cava	1 (1.1)
Axillar and femoral	1 (1.1)
BD clinical manifestations at the moment of the thrombotic episode[b]	
Oral ulcers	77 (71.9)
Genital ulcers	43 (40.2)
Cutaneous involvement	38 (45.2)
Pseudofolliculitis	32 (29.9)
Erythema nodosum	20 (18.7)
Arthritis	22 (20.6)
Ophthalmologic Involvement	20 (23.8)
Anterior uveitis	16 (14.9)
Retinal vasculitis	13 (12.1)
Posterior uveitis	11 (10.3)
Central nervous system involvement	33 (30.8)
Aseptic meningitis	4 (3.7)
Arterial aneurysm	4 (3.7)

[a]Considering the first thrombotic episode (n=91). [b]Results are referred to 107 episodes of venous thrombosis (7 [7.7%] patients were excluded due to the lack of relevant data).

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