Manifestations and predictors of vascular involvement in Behçet's disease

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Dear Editor,

Behçet's disease (BD) is a variable vessel vasculitis characterised by heterogeneous manifestations[1]. Vascular involvement (VBD) most often affects the venous system, occurring in up to 15-40% of patients[1-4]. Vascular manifestations are major predictors of morbidity and mortality in BD[5,6]. However, predictors of VBD remain poorly defined.

Our aim was to characterise VBD patients and identify its predictors. We conducted a single-centre, retrospective study, including patients fulfilling the 2013 International Criteria for BD, registered in the Rheumatic Diseases Portuguese Registry (Reuma.pt) between October 2014 and May 2023[7,8]. VBD was defined as an arterial or venous manifestation attributable to BD and confirmed by imaging (Doppler ultrasonography, computed tomography angiography, or magnetic resonance angiography), excluding ocular and central nervous system vascular involvement. Demographic and clinical characteristics were collected. Clinical manifestations were categorised as occurring at disease onset (within the first 12 months after symptom onset) or ever (at onset and/or at any time during follow-up). Comparisons were made using chi-squared, Fisher's exact, Mann-Whitney or t-test, with $p<0.05$ considered significant. A multivariable logistic regression model with backward stepwise selection was performed to determine predictors of VBD.

We included 157 BD patients. VBD was present in 24 (15%) and was the inaugural manifestation in seven (5%). VBD developed at a median age of 36.0 years (IQR 10.0), 8.9 median years (IQR 16.7) after BD symptom onset. The most frequent symptoms were limb pain (12/16, 75%), limb oedema (7/14, 50%) and thoracic pain (4/22, 18%). The venous system was more frequently involved than the arterial (20/24, 83% *vs* 10/24, 42%), with six patients exhibiting both. Venous involvement included deep vein thrombosis (12/24, 50%) and superficial thrombophlebitis (10/24, 42%). The lower limb veins were involved in all patients with venous disease (100%) and the inferior vena cava in one (5%). Arterial involvement included aneurysms (5/24, 21%), pulmonary thrombosis (3/24, 13%) and pseudoaneurysms (2/24, 8%). The pulmonary (4/10, 40%) and lower limb arteries (4/10, 40%) were most affected. Multiple-vessel involvement (13/24, 54%) and recurrent episodes (14/24, 58%) were frequent.

Disease characteristics of patients with BD with and without vascular involvement are presented in Table I. In univariable analysis, cutaneous manifestations at disease onset (OR 2.65, p=0.038) and constitutional symptoms during follow-up (OR 2.81, p=0.046) were associated with VBD, in addition to male sex and ocular involvement at onset (Table I). On multivariable analysis, only

male sex (OR 3.99, 95%CI 1.55-10.28) and ocular involvement at disease onset (OR 3.90, 95%CI 1.29-11.72) remained independently associated with VBD (Table I). A sensitivity multivariable analysis excluding individuals with VBD at baseline identified male sex as the only independent predictor of this manifestation (OR 4.61, 95% CI 1.59–13.4; p=0.005). Mortality did not significantly differ between groups (2/24, 8% *vs* 3/133, 2%; p=0.168).

In summary, our cohort showed a 15% prevalence of VBD, with deep vein thrombosis being the predominant form. Male sex and ocular manifestations at disease onset emerged as independently associated with VBD. Previous studies consistently reported a higher frequency of VBD in males[3,4,9,10], while ocular manifestations were usually described as less common in this group[3,4,9]. Associations with genital ulcers[3,9], gastrointestinal disease[3,10], erythema nodosum, cardiac and neurological involvement have been variably reported[3,4,9,10]. Our findings reinforce male sex as an independent predictor of VBD but, in contrast to prior reports, identify an independent association between ocular involvement at disease onset and VBD. This difference may reflect a geographical variation in disease phenotype, as earlier reports were from non-European populations[3,4,9,10]. Importantly, although vascular involvement is considered a marker of poor prognosis, no statistically significant difference in mortality was detected. This may reflect sample size limitations or follow-up differences between studies.

To our knowledge, this is the first European registry-based study to identify independent predictors of vascular involvement in BD. Strengths include its long observational period, while limitations include its retrospective design and relatively small sample size. The small number of VBD events resulted in imprecise effect estimates, as reflected by the wide confidence intervals. In addition, ocular involvement encompassed retinal vasculitis, which may have contributed to an overestimation of its association with VBD by capturing a possibly shared underlying vasculitic process across distinct vascular beds. Our findings suggest that male sex and ocular manifestations at disease onset may identify patients at higher risk of VBD, but further studies are needed to validate these predictors and clarify their role in risk-stratified management.

Tables and Figures

Table I. Patient-and disease-characteristics associated with vascular involvement in Behçet's disease – multivariable analysis

Variable	Univariable models OR (95% CI) (N=80-157)	Univariable models *p*-value	Multivariable model OR (95% CI) (N=153)
Male gender	**3.59 (1.46-8.82)**	**0.005**	**3.99 (1.55–10.28)**
Caucasian ancestry	0.57 (0.17-1.94)	0.379	†
Age at symptom onset (years)	0.99 (0.96-1.03)	0.758	‡
Oral ulcers at disease onset	1.37 (0.29-6.43)	0.690	†
Genital ulcers at disease onset	0.83 (0.33-2.10)	0.687	†
Ocular manifestations at disease onset	**3.63 (1.27-10.33)**	**0.016**	**3.90 (1.29–11.72)**
Cutaneous manifestations at disease onset	**2.65 (1.06-6.67)**	**0.038**	‡
Articular manifestations at disease onset	0.67 (0.14-3.14)	0.614	†
Neurological manifestations at disease onset	NA	NA	†
Gastrointestinal manifestations at disease onset	NA	NA	†
Constitutional symptoms at disease onset	0.54 (0.07-4.44)	0.567	†
Oral ulcer (ever)	NA	NA	†
Genital ulcers (ever)	1.22 (0.38-3.86)	0.741	†
Ocular manifestations (ever)	2.16 (0.90-5.20)	0.085	†
Cutaneous manifestations (ever)	4.28 (0.96-19.13)	0.057	†
Articular manifestations (ever)	0.55 (0.22-1.37)	0.197	†
Neurological manifestations (ever)	1.57 (0.52-4.70)	0.424	†
Gastrointestinal manifestations (ever)	0.72 (0.15-3.35)	0.670	†
Constitutional symptoms (ever)	**2.81 (1.02-7.77)**	**0.046**	‡
Positive pathergy test	1.09 (0.33-3.67)	0.885	†
Positive HLA-B51 haplotype	0.70 (0.19-2.61)	0.596	†

Variables selected for multivariable models if p-value<0.05 in univariable analysis.
† Not entered into multivariable analysis; ‡ Variables which were tested in the regression models but not retained after backward selection; NA, not applicable.

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