Manifestations and predictors of neurologic involvement in Behçet's disease

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Dear Editor,

Behçet's disease (BD) is a multisystem inflammatory disorder of unclear aetiology, exhibiting a broad spectrum of clinical manifestations. Neurological involvement, termed neuro-Behçet's disease (NBD), varies widely in prevalence (1-59%) and significantly increases morbidity and mortality[1-7]. Central nervous system (CNS) involvement is more frequent than peripheral involvement and is categorized into parenchymal or non-parenchymal phenotypes[1-8]. Diagnosis relies on clinical presentation, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings, as outlined by the International Consensus Recommendation (ICR) Criteria[8]. High clinical suspicion is essential, especially when NBD is the initial manifestation of BD or MRI findings are unremarkable[1,5-7]. In addition, limited and conflicting data exist regarding the associations between clinical manifestations and neurological involvement in BD[5,7,9]. Our objective was to characterize patients with BD and CNS involvement who were followed at a single academic hospital and to identify predictors of this clinical subtype. We conducted an observational, 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[10]. NBD was defined according to the ICR Criteria[8]. Demographic, clinical and treatment data were collected. Comparisons were made using T-tests, Mann-Whitney and Chi-squared tests with a significance threshold of $p<0.05$. Independent associations were tested using a multivariable logistic regression model.

A total of 157 BD patients were included (Table I), 116 (74%) of them were females and 127 (81%) Caucasian, of whom 24 were diagnosed with NBD. The mean±SD age at BD diagnosis was 32.0±12.2 years and the median (IQR) follow-up was 11.0 (11.8) years. Of the 24 (15%) patients diagnosed with NBD, two (1%) were identified at disease onset. The mean age at NBD diagnosis was 31.6±8.7 years, occurring 4.7 (1.0) years after BD onset. Headache was the most frequent symptom (71%) and 19 (79%) patients experienced a single episode of NBD. Among NBD patients, 15 (63%) had parenchymal, eight (33%) non-parenchymal and one (4%) mixed CNS involvement (aseptic meningitis and rhombencephalitis). Imaging abnormalities were identified in 22 (96%) patients and CSF abnormalities in six (55%). Compared to patients without NBD, those with NBD were more likely to be non-Caucasian (27% *vs* 17%, p=0.026), have genital ulcers at disease onset (68% *vs* 34%, p=0.002) and present with ocular manifestations during the disease course (58% *vs* 35%, p=0.028). NBD patients more frequently received systemic glucocorticoids (100% *vs* 78%, p=0.008) and conventional synthetic disease-modifying anti-rheumatic drugs (86% *vs* 62%, p=0.035), particularly cyclophosphamide (48% *vs* 1%, p<0.001).

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Mortality was also significantly higher among NBD (13% *vs* 2%, p=0.026). Genital ulcers at presentation (OR 4.50, 1.68-12.06) and ocular involvement during the disease course (OR 2.69, 1.01-6.76) were independent predictors of CNS involvement (Table S1).

In summary, our cohort showed a 15% prevalence of CNS involvement, with parenchymal affection being the predominant form. The elevated mortality rate found among these patients underscores the severity of NBD and the critical need for prompt recognition. Genital ulcers at onset and ocular manifestations emerged as independent predictors of NBD, serving as potential clinical markers for identifying high-risk patients. Our findings align with prior studies despite the ethnic variations among populations[5,7,9]. Houman *et al.* reported a higher frequency of genital ulcers and lower HLA-B51 positivity in NBD patients, while Ideguchi *et al.* observed greater ocular involvement but fewer genital ulcers, particularly among males with NBD[5,7,9]. These differences highlight the heterogeneity of NBD across various groups. This study is limited by its retrospective design, small sample size and potential underestimation of CNS involvement due to diagnostic challenges. Nonetheless, our results emphasize the importance of identifying early predictors of NBD to improve risk stratification and clinical management. Prospective, multicentre studies are warranted to confirm our findings and refine management strategies.

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Tables and Figures

Table I – Disease characteristics of patients with Behçet's disease with and without central nervous system involvement.

	All patients (N=157)	NBD patients* (N=24)	Non-NBD patients (N=133)	*p*-value
Demographics				
Male gender, n (%)	41 (26)	6 (25)	35 (26)	0.893
Caucasian ancestry, n (%)[θ]	127 (81)	16 (73)	111 (83)	**0.026**
Age at symptom onset, mean±SD years[θ]	24.5±12.5	27.4±9.7	24.0±12.9	0.150
Age at BD diagnosis, mean±SD years[θ]	32.0±12.2	31.6±8.7	32.1±12.8	0.798
Diagnostic delay, median (IQR) years[θ]	3.0 (8.0)	1.8 (9.2)	3.0 (11.9)	0.303
Symptom duration, median (IQR) years[ϕ]	11.0 (11.8)	11.5 (18.0)	11.0 (11.0)	0.934
Manifestations at disease onset, n (%)				
Oral ulcers[θ]	136 (89)	20 (91)	116 (89)	1.000
Genital ulcers[θ]	59 (39)	15 (68)	44 (34)	**0.002**
Ocular manifestations[1θ]	21 (16)	6 (27)	15 (11)	0.085
Cutaneous manifestations[2θ]	39 (26)	6 (27)	33 (25)	0.742
Articular manifestations[3θ]	18 (12)	1 (5)	17 (13)	0.470
Vascular manifestations[4θ]	6 (4)	2 (10)	4 (3)	0.194
Gastrointestinal manifestations[5θ]	1 (1)	0	1 (1)	NA
Constitutional symptoms[θ]	11 (7)	0	11 (8)	NA
Manifestations at both disease onset and follow-up, n (%)				
Oral ulcer	152 (97)	23 (96)	129 (97)	0.569
Genital ulcer	127 (81)	19 (79)	108 (81)	0.782
Ocular manifestations[1θ]	60 (38)	14 (58)	46 (35)	**0.028**
Cutaneous manifestations[2θ]	117 (75)	17 (71)	100 (76)	0.608
Articular manifestations[3θ]	71 (46)	11 (46)	60 (45)	0.973
Vascular manifestations[4θ]	24 (15)	5 (21)	19 (14)	0.373
Gastrointestinal manifestations[5]	17 (11)	2 (8)	15 (11)	1.000
Constitutional symptoms	24 (15)	7 (29)	17 (13)	0.060
Positive pathergy test[▽]	33 (37)	8 (62)	25 (32)	0.062
Positive HLA-B51 haplotype[▽]	35 (44)	6 (50)	29 (43)	0.636
ISG, 1990 criteria fulfilment	122 (78)	19 (79)	103 (77)	0.852
ICBD, 2006 criteria fulfilment	146 (93)	24 (100)	122 (92)	0.217
Treatment during the disease course, n (%)				

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Systemic glucocorticoids$^{\phi}$	126 (81)	23 (100)	103 (78)	**0.008**
csDMARD$^{\phi}$	100 (65)	18 (86)	82 (62)	**0.035**
bDMARD$^{\phi}$	22 (15)	6 (29)	16 (12)	0.087
Cyclophosphamide$^{\phi}$	12 (8)	10 (48)	2 (1)	**<0.001**
Prognosis, n (%)				
Mortality	5 (3)	3 (13)	2 (2)	**0.026**

BD, Behçet's disease; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CNS, central nervous system; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; ICBD, International Criteria for Behçet´s Disease; ISG, International Study Group for Behçet's; NA, not applicable; NBD, neuro-Behçet´s disease.

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions.
* Two of the NBD patients were classified as having probable NBD; the remaining ones had a definitive NBD diagnosis. θ Missing data <10%; ϕ Missing data 10-20%; ∇ Missing data 25-50%.
[1]Ocular manifestations included anterior and/or posterior uveitis, retinal vasculitis and central retinal vein or artery occlusion; [2]Cutaneous manifestations included erythema nodosum, pseudofoliculitis and papulopustular or acneiform lesions; [3]Articular manifestations included inflammatory arthralgia and arthritis; [4]Vascular manifestations included superficial phlebitis, deep vein thrombosis, large vein thrombosis and arterial thrombosis or aneurysm; [5]Gastrointestinal manifestations included abdominal pain, diarrhoea, bowel obstruction and bowel perforation.

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Supplementary Material

Table S1: Patient and disease characteristics associated with central nervous system involvement in Behçet's disease – multivariate analysis.

Variable	Univariable models OR (95% CI) (N=80-157)	Univariable models *p*-value	Multivariable model OR (95% CI) (N=153)
Male gender	0.93 (0.34-2.54)	0.893	†
Caucasian ancestry	**0.26 (0.09-0.81)**	**0.020**	†
Age at disease onset (years)	1.02 (0.99-1.06)	0.232	†
Oral ulcers at disease onset	1.29 (0.28-6.09)	0.745	†
Genital ulcers at disease onset	**4.24 (1.61-11.15)**	**0.003**	**4.50 (1.68-12.06)**
Ocular manifestations at disease onset	2.90 (0.98-8.55)	0.054	†
Cutaneous manifestations at disease onset	1.19 (0.43-3.31)	0.742	†
Articular manifestations at disease onset	0.34 (0.04-2.66)	0.301	†
Vascular manifestations at disease onset	3.34 (0.57-19.51)	0.180	†
Gastrointestinal manifestations at disease onset	0	NA	NA
Constitutional symptoms at disease onset	0	NA	NA
Oral ulcer (ever)	0.71 (0.08-6.67)	0.767	†
Genital ulcer (ever)	0.88 (0.30-2.58)	0.815	†
Ocular manifestations (ever)	**2.65 (1.09-6.43)**	**0.031**	**2.69 (1.01-6.76)**
Cutaneous manifestations (ever)	0.78 (0.30-2.04)	0.609	†
Articular manifestations (ever)	1.02 (0.42-2.43)	0.973	†
Vascular manifestations (ever)	1.58 (0.53-4.74)	0.415	†
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	3.33 (0.99-11.22)	0.052	†
Positive HLA-B51 haplotype	1.35 (0.39-4.60)	0.637	†

Variables selected for multivariable models if p-value<0.05 in univariable analysis.
† Not selected for multivariable analysis (p-value>0.05); NA, not applicable.

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