Adamantiades-Behçet Disease at the Beginning of the Silk Route: North-East Italian Experience

Dear Editor,

Adamantiades-Behçet's disease (ABD) is an inflammatory disease classified as vasculitis, which was originally diagnosed in patients with aphthous stomatitis, genital ulcerations, and ocular manifestations. However, any organ or system may be involved, particularly the central and peripheral nervous systems, joints, as well as the gastrointestinal tract. The etiology of ABD is still not fully understood, but some evidence indicates that an autoimmune process could be triggered by an infectious or environmental agent specific for the geographic region (1). Although BD can occur worldwide, it is most prevalent in the region along the ancient commercial route called the "Silk Road". In Italy, studies on the precise prevalence of ABD are lacking (2). As there are no specific diagnostic laboratory tests or histopathologic findings which confirm the preliminary diagnosis, the final diagnosis should be based on clinical criteria (3). Skin and mucosae are the target organs of this disease, and therefore their involvement has been considered in the numerous diagnostic criteria developed over the years (4). The first most important and popular criteria were created in 1990 by the International Study Group (ISG) (5). Because of their low sensitivity, the new International Criteria for Behçet's Disease (ICBD) were established, and were presented at the International Conference of Behçet's Disease in Lisbon in 2006 (6,7). In 2014, the International Team for the Revision of the International Criteria for BD submitted new criteria assigning 2 points to ocular lesions, oral aphthosis, and genital aphthosis, and 1 point to skin lesions, central nervous system involvement, and vascular manifestations. The pathergy test, when used, was assigned 1 point. A patient scoring ≥4 points is classified as having BD (8). We performed a single center, case-control study on a cohort of patients of Friuli Venezia Giulia, enrolled from January 2010 to September 2015 in the Dermatology Unit of the University of Trieste. The aim was to analyze the clinical features and compare the sensitivity, specificity, and accuracy of the three diagnostic criteria for ABD presented above in patients born in this particular region which is located at the very start of the "Silk Route".

We enrolled 153 consecutive patients (74 cases and 79 controls) in the study. The characteristics and clinical features of patients and controls are summarized in Table 1. The most common diagnoses in the control group were recurrent oral aphtosis, lichen planus, mucous-membrane pemphigoid, and lupus erythematosus. The inclusion criterion was the presence of at least one principal clinical feature of ABD (oral aphtosis, genital aphtosis, skin lesions, ocular involvement) properly recorded in clinical records. Patient recruitment was done in a consecutive manner. Exclusion criteria were incomplete clinical records and absence of follow-up data.

The diagnosis of ABD was established by expert dermatologists, without the use of any particular diagnostic criterion. For ABD, diagnosis agreement among dermatologists was required. The study was conducted according to the Declaration of Helsinki protocols.

Possible associations between categorical variables were detected by the use of Fisher's exact test or Pearson χ^2 test, depending on the sample size. Logistic regression was performed in order to identify which symptoms are of higher impact in the diagnosis of ABD. A comparison in terms of sensitivity, specificity, and accuracy among the three diagnostic criteria (ISG 1990, ITR 2006, and ITR 2014) was performed. The receiver operator characteristic (ROC) curve was obtained for each diagnostic criterion.

Data were produced with a 95% confidence interval; P values <0.05 were considered statistically significant. Statistical analysis was done using Stata SE12 software (Stata Corporation, Tx, USA).

According to our data, patients with ABD had a significantly lower age at diagnosis compared with controls (P=0.0001); this was confirmed for both men (P=0.0006) and women (P=0.004). The presence of oral aphtosis was not necessarily pathognomonic of ABD (P=0.005) as it was found in 97.3% of patients with ABD and in 83.5% of controls. Genital aphtosis was directly associated with ABD diagnosis (P<0.001),

Table 1. Comparison between the clinical characteristics of patients and controls

	Behçet Disease (n=74, M=21, F=53)	Controls (n=79, M=13, F=66)	*P* value
Age	45.79 ± 13.25	56.09 ± 17.78	0.0001
Age if Male	42.78 ± 11.71	62.43 ± 20.55	0.0006
Age if Female	46.98 ±13.73	54.84 ± 17.08	0.0038
Oral aphtosis	72 (97.30%)	66 (83.54%)	0.005
Genital aphtosis	59 (79.73%)	7 (8.86%)	0.000
Skin manifestations	46 (62.16%)	22 (27.85%)	0.000
Pseudofolliculitis	33 (44.59%)	13 (16.46%)	0.000
Erythema nodosum	18 (24.32%)	10 (12.66%)	0.093
Cutaneous aphtosis	1 (1.35%)	0 (0.00%)	0.484
Ocular lesions	16 (21.62%)	4 (5.06%)	0.003
Anterior uveitis	14 (18.92%)	2 (2.53%)	0.001
Posterior uveitis	4 (5.41%)	2 (2.53%)	0.0431
Retinal vasculitis	1 (1.35%)	1 (1.27%)	0.963
Joint manifestations	34 (45.95%)	32 (40.51%)	0.518
Arthralgia	27 (36.49%)	25 (31.65%)	0.609
Arthritis	7 (9.46%)	7 (8.86%)	0.898
Spondylitis	1 (1.35%)	1 (1.27%)	0.963
Neurological manifestations	11 (14.86%)	4 (5.06%)	0.056
Peripheral	5 (6.76%)	4 (5.06%)	0.740
Central	6 (8.11%)	0 (0%)	0.011
Vascular manifestations	10 (13.51%)	3 (3.80%)	0.042
Arterial thrombosis	1 (1.35%)	0 (0%)	0.484
Venous thrombosis	3 (4.05%)	1 (1.27%)	0.354
Phlebitis	7 (9.46%)	3 (3.80%)	0.1999
Gastrointestinal manifestations	11 (14.86%)	0 (0.00%)	0.000
Epididymitis	2 (2.70%)	0 (0.00%)	0.232
Pathergy test positive	17 (36.17%)	1 (4.76%)	0.007
HLA B51 test positive	26 (70.27%)	9 (34.62%)	0.009

as it was present in 79.7% of patients with ABD, but in only 8.9% of controls. Furthermore, even skin manifestations and ocular lesions were observed at different rates in patients with ABD and controls (*P*<0.001 and *P*=0.003, respectively). The presence of pseudofolliculitis was significantly more frequent in patients than in controls (*P*<0.001), whereas erythema nodosum and skin aphtosis did not differ considerably between ABD and controls. Joint manifestations were as common in patients with ABD as in controls (*P*=0.6): arthralgia and arthritis alone do not indicate

a diagnosis of ABD. Neurological symptoms as well as vascular involvement, if present, can be suggestive of ABD, but their absence does not exclude an ABD diagnosis (*P*=0.06 and *P*=0.04). Positive pathergy tests and positive HLA B51 tests were significantly more frequent in patients than in controls (*P*=0.007 and

Table 2. Results of logistic regression

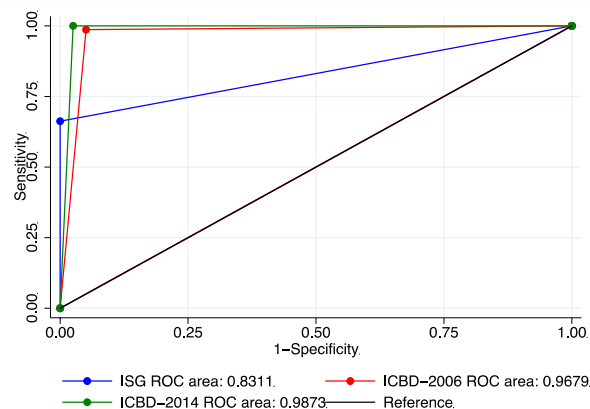| Clinical Features	Odds ratio	*P* value
Younger age	0.8950334	0.000
Oral aphtosis	145.3229	0.004
Genital aphtosis	12947.7	0.000
Skin involvement	104.5625	0.002
Neurological inolvement	819.263	0.001
Vacular involvement	240.2573	0.000

Figure 1. Results of receiver operator characteristic (ROC) areas.

P=0.009, respectively), although if negative they did not exclude a diagnosis of ABD.

Logistic regression showed that genital aphtosis (odds ratio (OR)=12948, *P*<0.001), neurological manifestations (OR=819.263, *P*=0.001), vascular manifestations (OR=240.2573, *P*=0.001), cutaneous manifestations (OR=104.5625, *P*=0.002), oral aphtosis (OR=145.3229, *P*=0.004), and younger age at diagnosis (OR=0.8950334, *P*=0.000) were associated with ABD diagnosis (Table 2). There was no single pathognomonic symptom of ABD.

We found that the ITR criteria –both from 2006 and 2014 – had a higher sensitivity (98.7% and 100%, respectively), specificity (94.9% and 97.9%, respectively), and accuracy (96.7% and 98.7%, respectively) compared with the ISG 1990 criterion, which scored 66% sensitivity, 100% specificity, and 83.7% accuracy. Area Under Roc Curve (AUC) was significantly different between ISG 1990 and ITR 2006 and between ISG 1990 and ITR 2014 (Figure 1). Even though no statistically significant difference was found between the ITR 2014 and ITR 2006 criteria, the former had a better performance according to our records.

The clinical features reported in our retrospective case-control study are comparable to data found in the literature from European and international reports.

A recent study (8) found a similar organ involvement percentage to our study, although we found a higher prevalence of HLA B51 positive patients and a lower percentage of ocular manifestations in our records. The results of the logistic regression performed based on our records indicate genital aphtosis, oral aphtosis, ocular involvement, neurological signs, and vascular features are more strongly linked to the diagnosis of ABD. According to our data, the presence of oral aphtosis is not paramount for the diagnosis of ABD, which fits well with the intent of the ITR 2006 and 2014 diagnostic criteria. The new ITR 2014 criteria added neurological signs to the diagnostic symptoms of ABD, emphasizing the importance of a multidisciplinary approach to patients suspected to have ABD.

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