Are clusters of patients with distinct clinical expression present in Behçet's disease?

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ABSTRACT

Objective. *Studies from Israel and Turkey have proposed that patient clusters with discriminating clinical features may exist in Behçet's disease (BD); such clusters could help to better understand pathogenetic mechanisms and guide therapeutic decisions. Herein, we searched for specific associations between each disease manifestation to all other manifestations in Greek patients with BD.*

Methods. *Specific clinical features were retrospectively recorded in 142 consecutive patients (80 men) fulfilling the International Study Group criteria, seen between 2000-2008 in our Departments (mean follow-up of 37 months). All possible associations between distinct clinical features were examined; further analysis in relation to HLA-B51 status and pathergy test positivity, available in 89 patients, was performed.*

Results. *No significant associations between various manifestations of BD were found, either among all patients, or among men or women analysed separately. Uveitis was present more frequently in men, but not women, who were HLA-B51 carriers ($p<0.02$). A positive pathergy reaction was associated with oral ulcers ($p<0.001$) and central nervous involvement ($p=0.008$) in women, and folliculitis in men ($p=0.046$).*

Conclusion. *In contrast to studies from other countries, no subgroups of patients with distinct positive or negative associations between clinical features were found. HLA-B51 may have some prognostic significance in men only. Whether differences in disease expression between geographical areas may reflect different triggers of pathogenetic mechanisms operating among ethnic groups could be further explored in comparative studies.*

Introduction

Behçet's disease (BD) is a chronic multisystem inflammatory disorder of unknown etiology, which is classified among the vasculitides. It is spread worldwide, with a higher prevalence rate in countries along the ancient Silk Route (Far and Middle East and Mediterranean countries) (1). Recent findings suggest that BD, although uncommon in Central and Northern Europe, has a higher prevalence than currently thought (2). The typical onset of the disease is the 3rd decade, but can occur at any age. It affects both genders, however, frequency and disease severity varies. (3) Genetic, environmental, immunologic, haemostatic and rheological factors are involved in the aetiopathogenesis of the disease (1). Most widely held hypothesis is that BD represents the result of an (auto)immune reaction triggered by an infectious agent in a genetically predisposed individual (4).

BD has a wide spectrum of clinical manifestations and an unpredictable evolution with repeated periods of exacerbations and remissions, severity and frequency of which may diminish with time (5). Any vasculised organ may be affected and systemic involvement may portend a poorer prognosis. Recurrent oral ulceration is the most characteristic symptom and the presenting one in most cases. Genital ulcers, which are often painful, and ocular inflammation, are less frequent but characteristic of the disease. The clinical picture of BD also includes inflammation of the skin (erythema nodosum, folliculitis), arthritis, thrombophlebitis, gastrointestinal and neurologic manifestations (6). The clinical presentation is diverse, with important differences not only between men and women (3, 6), but also between children and adults (3, 7). Alhtough not always accepted, some studies have also proposed a ethnogeographic influence in disease expression (2, 8, 9). For example, a positive pathergy reaction is of diagnostic importance in Turkey and Japan, whereas it is rare in patients in Nothern Europe and USA (5). On the

other hand, neurological involvement is more common in European and American patients than patients from Turkey, whereas intestinal involvement is frequent in Japan but not in Turkey and Tunisia (5, 8, 10, 11).

Despite heterogeneity in clinical disease expression, there are studies suggesting positive and negative associations between certain clinical findings, which result to specific disease clusters (10-12). For example, a Turkish study (10) revealed a positive association between oral and genital ulcers and erythema nodosum, while uveitis was negatively associated with erythema nodosum only among the females. Another study in patients from Israel (11) demonstrated an association between folliculitis and genital ulceration, which were inversely correlated with uveitis. Moreover, increased presence on enthesopathy among patients with acne and arthritis has been reported (12). Herein, we aimed to search for specific positive or negative associations between each disease manifestation to all other manifestations, implying clusters with distinct clinical expression in Greek patients with BD. Identification of such associations could help us not only to better understand the pathogenesis of the disease, but also to guide therapeutic decisions.

Patients and methods

One hundred and forty two consecutive patients (80 men), fulfilling the International Study Group criteria for BD (13), who were seen in our Departments between 2000 and 2008 were included in this retrospective study, irrespective of disease duration. Duration of disease was 13.7±1.9 (mean±SD) years (13.4±2.4 for men and 14.1±3.1 for women) and follow-up was 37±4.4 months (36.6±5.8 for men, 37.4±6.8 for women, ranging from 2 to 102 months). In addition to any symptom present at disease onset, the following specific clinical features were recorded if present after 2000: oral/genital ulcers, erythema nodosum, folliculitis, arthritis, thrombophlebitis, uveitis, gastrointestinal and neurological manifestations. Data on either pathergy test or HLA-B51 status were present in 89 patients (pathergy test: 49 men and 40 women, HLA B51: 42 men and 47 women). Statistical analysis was performed using Chi-square tests with Yate's correction for the comparison of 2×2 frequency tables in subgroups of patients with or without specific manifestations under study.

Table I. Frequency of specific clinical features in patients with BD during follow-up (mean of 37 months).

	All (%)	Men (%)	Women (%)	p^*
n	142	80 (56,3)	62 (43,7)	
Age (mean ± SD)	35.01 ± 2.17	34.52 ± 3.08	35.65 ± 3.06	NS
Age at disease onset (mean ± SD)	25.58 ± 2.16	25.01 ± 2.86	26.3 ± 3.31	NS
Oral ulcers	126 (89)	68 (85)	58 (93.5)	0.110
Genital ulcers	84 (59.2)	53 (66.3)	29 (46.8)	**0.020**
Erythema nodosum	35 (24.6)	20 (25)	15 (24.2)	0.912
Joint involvement	86 (60.6)	46 (57.5)	40 (64.5)	0.396
Thrombophlebitis	13 (9.2)	10 (12.5)	3 (4.8)	0.116
Intestinal involvement	18 (12.7)	9 (11.3)	9 (14.5)	0.562
Uveitis	81 (57)	47 (58.8)	34 (54.8)	0.641
Central nervous system involvement	35 (24.6)	19 (23.8)	16 (25.8)	0.778
Folliculitis	63 (44.4)	49 (61.3)	14 (22.6)	**<0.000**

*Denotes differences between men and women.

Results

Demographic characteristics and the frequency of specific clinical manifestations during follow-up are shown in Table I. Oral ulceration was not only the most frequent symptom during follow-up in either men or women (85% and 93.5%, respectively, Table I), but also the most frequent onset sign (data not shown). The most frequent second sign was genital ulceration for men (66.3%) and joint involvement for women (64.5%). Genital ulcers and folliculitis were more frequent among male patients (66.3% *vs*. 46.8% p=0.02 and 61.3% *vs*. 22.6%, p=0.001, respectively). There were no significant differences in the frequency of any other manifestations between male and female patients.

The presence of positive or negative associations was examined in all patients, as well as in men and women separately (36 pairs of clinical symptoms in men, 36 in women and 36 in total study population). Thus, taking in account the presence of oral ulcers, genital ulcers, erythema nodosum, folliculitis, arthritis, thrombophlebitis, ocular, gastrointestinal and neurological involvement, no disease clusters of patients with distinct clinical expression were found (non-statistically significant associations between all 108 pairs of symptoms examined, data not shown).

Subsequently, the presence of HLA-B51 and the positive pathergy reaction was included in the analysis. Mean age and mean age at disease onset were similar between subgroups of patients with positive or negative pathergy reaction, as well as between subgroups with different HLA B51 status. We found no association between HLA B51 positivity and positive pathergy reaction, either in the total of patients, or within men or women. As shown in Table II, HLA-B51 carriers had more frequently uveitis, not only in the total population but also in men separately (p=0.013 and p=0.017, respectively). On the other hand, as shown in Table III, a positive pathergy reaction was strongly associated with oral ulcers in all patients and especially in females (p<0.001 for both). Moreover, there was an association between positive pathergy reaction and folliculitis in male patients alone (0.046) as well as with central nervous system involvement in females (0.008).

Finally, an additional analysis was performed taking in account symptoms present at disease onset together with clinical features present after 2000. Similarly, non-statistically significant associations between all pairs of clinical symptoms examined were found. On the other hand, HLA-B51 carriers had again more frequently uveitis

Table II. Specific clinical features present in patients with BD in relation to HLA-B51 status.

	All patients n=89		Men n=42		Women n=47	
HLA-B51	+	--	+	--	+	--
Oral ulcers	55	26	30	8	25	18
Genital ulcers	37	16	23	8	14	8
Erythema nodosum	14	4	7	2	7	2
Joint involvement	44	17	24	5	20	12
Thrombophlebitis	4	3	2	2	2	1
Intestinal involvement	8	4	3	1	5	3
Uveitis	**43***	12	**25****	3	18	9
Central nervous system involvement	10	9	5	2	5	7
Folliculitis	27	12	22	7	5	5
Pathergy +	24	9	11	3	13	6

*p=0.013 and **p=0.017 *vs*. HLA-B51 negative patients.

Table III. Specific clinical features present in patients with BD in relation to pathergy test.

	All patients n=89		Men n=49		Women n=40	
Pathergy test	+	--	+	--	+	--
Oral ulcers	**41***	24	21	24	**20****	0
Genital ulcers	27	25	18	18	9	7
Erythema nodosum	12	11	8	6	4	5
Joint involvement	24	28	11	16	13	12
Thrombophlebitis	6	5	4	4	2	1
Intestinal involvement	4	5	1	4	3	1
Uveitis	25	31	13	18	12	13
Central nervous system involvement	12	7	4	6	**8*****	1
Folliculitis	22	18	**17******	15	5	3
HLA B51 +	24	20	11	13	13	7

*p<0.001, **p<0.001, ***p=0.008, ****p=0.046 *vs*. patients with negative pathergy test.

(p=0.018 and p=0.004 in the total population and in men separately, respectively). The associations between positive pathergy reaction and folliculitis in male patients alone, as well as with central nervous system involvement in females, remained significant (p=0.046 and p=0.008, respectively). The significant association between the positive pathergy reaction and oral ulcers (occurring during follow-up) was lost, since the latter feature was present in 100% of patients.

Discussion

The clinical picture of Greek patients with BD was studied to further explore whether there are distinct patterns of disease expression. Our data do not confirm previous studies suggesting that disease clusters are present in BD. Associations between folliculitis/genital ulceration and papulopustular rash/gastrointestinal symptoms reported in Israeli patients (11), or associations between oral/genital ulcers/erythema nodosum and papulopustular skin lesions/joint involvement found in Turkish patients (10) were not present in our patients. Notably, these two studies present different associations between the various clinical manifestations of patients with BD. This is possibly due to speciifc factors, including methodology differences.

Firstly, Tunc *et al*. limited the time of symptom recording to 3 months, as they considered that clinical associations that occurred together at the same time would be pathogenically more closely related (10). On the other hand, Krause *et al*. included data on all recorded disease manifestations, at any time, in a retrospective manner (11). Thus, their results may not be applicable to the characterization of patients at disease onset, but only during disease evolution. In our study, a similar methodology was applied, as we recorded any symptom between 2000 and 2008, albeit for a different period of time for each patient.

Secondly, there is an important differentiation concerning the age of patients included in each study which may influence the results. A large number of patients included in Krause's study were pediatric patients (11), whereas Tunc's study was conducted only among adult patients (10). In our study, there are 6 young patients: 8, 11, 14, 15, 15 and 17 years old. Children with BD may have a different clinical picture than adults, *i.e*. uveitis and genital ulcers are less frequent in children, whereas neurological involvement is much more often (6).

Finally, we applied a different statistical method than Tunc *et al*. (10) and Krause *et al*. (11). The chi-square statistical test was used herein because it was felt that factor analysis employed in the two previous studies was not appropriate. Factor Analysis seeks to find the latent factors that account for the patterns of collinearity among multiple metric variables. This analysis is appropriate when the following assumptions are fulfilled: 1) large enough sample to yield reliable estimates of the correlations among the variables, 2) statistical inference is improved if the variables are multivariate normal, 3) relationships among the pairs of variables are linear, 4) absence of outliers among the cases, 5) some degree of collinearity among the variables but not an extreme degree or singularity among the variables. To determine the factorability of an intercorrelation matrix, 2 tests are used, namely the Bartlett's Test of Sphericity, and the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) (14, 15). By applying these tests to our data we found that factor analysis was not appropriate (Bartlett's Test of Sphericity: χ^2=30.1, df=36, p=0.744, KMO=0.467). Nevertheless, factor analysis of our patients' data yielded 4 factors with eigenvalues

greater than 1, explaining 53.6% of the total variance. These were a) oral ulcers – joint involvement – thrombophlevitis, b) genital ulcers – erythema nodosum – folliculitis, c) CNS involvement – intestinal involvement and d) uveitis.

Although many authorities in the field believe that HLA-B51 status lacks diagnostic and prognostic significance we found that HLA-B51 positivity was associated with uveitis, but not with any other clinical feature of BD. The relationship between HLA-B51 and the severity of the disease has been suggested by Japanese investigators (16), but other studies did not confirm this association (3, 17). On the other hand, positivity of pathergy reaction in our patients was associated with oral ulcers, the hallmark of the disease, further adding to the diagnostic importance of pathergy reaction (18), which was also associated with folliculitis in male and neurological manifestations in female patients.

Conclusion

Ethnic differences and/or different geographical areas seem to be the most important factor(s) determining the presence of specific disease clusters in BD. Previous studies have also shown variations in the frequency of symptoms between populations (1). The relative genetic homogeneity of the Greek population can potentially explain the absence of disease clusters of BD in our country. Even though prospective studies from other counties are needed, it appears that ethnic differences have a significant impact on clinical expression of BD. Perhaps the possibility that different triggers of pathogenetic mechanisms, which however lead to a relatively common phenotype, operate in different geographical areas should be examined in comparative studies.

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