RHEUMATOLOGY

Rheumatology 2012;51:1053–1060
doi:10.1093/rheumatology/ker423
Advance Access publication 27 January 2012

Original article

The papulopustular lesion/arthritis cluster of Behçet's syndrome also clusters in families

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Abstract

Objective. We have previously reported distinct symptom clusters among our patients with Behçet's syndrome (BS). The presence of such clusters suggests that more than one pathogenetic mechanism might be operative in BS. Increases in the frequency of certain clusters in familial BS cases, if present, would further support this notion. To test this hypothesis, we compared the frequency of symptom clusters between familial (Group F) and non-familial (Group NF) cases of BS.

Methods. We identified 380 BS patients who had reported a first-degree relative by reviewing 6031 patient charts. We were able to contact 186 (Group F). From the same initial pool, 500 patients were randomly selected. Of those, patients who did not report a family history of BS and who had attended our clinic during the previous 3 months made up Group NF ($n = 221$). Both groups were questioned about their symptoms within the previous 3 months. Data were analysed using factor analysis, cluster analysis and χ^2 tests.

Results. The make-up of the symptom clusters were very similar for the factor and the cluster analyses. The frequency of papulopustular lesions and joint involvement cluster was significantly higher in Group F (39.2 *vs* 21.5%, $P < 0.001$). Furthermore, the same cluster was shared in 5/17 related pairs from Group F and in only 5/110 unrelated pairs from Group NF [29 *vs* 4.5%, $P = 0.004$; risk ratio (RR) = 6.47, 95% CI 2.15, 18.89].

Conclusion. The papulopustular lesions and arthritis cluster in BS appears to cluster in familial BS as well. This further supports the notion that the pathogenesis of BS may entail several distinct mechanisms resulting in separate phenotype clusters.

Key words: Behçet's syndrome, factor analysis, disease clustering.

CLINICAL SCIENCE

Introduction

Evidence for a genetic component in Behçet's syndrome (BS) includes increased familial aggregation with increased sibling recurrence ratios, the presence of genetic anticipation and the HLA-B51 association [1–4]. Recently in a genome-wide association study, in addition to confirming the HLA-B51 association, an independent association within the MHC Class 1 region and associations at IL10 and the IL23R-IL12RB2 locus were also identified [5].

A number of studies conducted in our unit pointed to clusters of disease expression in BS. Diri *et al*. [6] showed that BS patients with arthritis are more likely to have papulopustular skin lesions. The presence of this cluster was also verified in a factor analysis study in which additional symptom clusters were detected [7]. A more recent study by Hatemi *et al*. [8] indicated that enthesopathy was also a part of the papulopustular lesion + arthritis symptom cluster. The presence of different symptom clusters raises the possibility that the pathogenesis of BS involves more than one biologic pathway, as is probably true for certain other rheumatological diseases as well [9]. An increase in the observed frequency of said clusters in familial BS cases would provide additional evidence for the existence of such different pathways. To test this hypothesis, we compared the frequency of symptom clusters between familial (Group F) and non-familial (Group NF) cases of BS.

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Submitted 4 May 2011; revised version accepted 16 November 2011.

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Methods

The study was conducted at the dedicated multidisciplinary Behçet's Syndrome Research Center at Istanbul University Cerrahpasa Faculty of Medicine in Turkey. Among the 6031 charts manually reviewed, 380 patients reported having at least one first-degree relative with clinically diagnosed BS. All 380 patients fulfilled the International Study Group for Behçet's Disease criteria and had an established diagnosis of BS [10]. We were able to contact 186 of these 380 patients, and evaluated them either in our outpatient clinic [$n = 51$ (27.4%)] or interviewed them on the phone [$n = 135$ (72.6%)]. We confirmed that all had at least one first-degree relative with BS. These 186 patients formed the familial group (Group F). Seventeen first-degree relative pairs (14 siblings and 3 offspring–parent pairs) were identified in Group F. None of these 34 patients reported a second-degree or more distant relative with BS. Apart from these 34 patients, there were 152 patients in Group F whose relative with BS was not registered in our clinic. We did not try to contact or obtain information from this last group of individuals, and they were excluded from our survey.

We questioned, with a standard questionnaire, the 186 patients in Group F about clinical manifestations related to BS that they may have experienced during the preceding 3 months. Eye, vascular, neurological and gastrointestinal manifestations were noted as positive only if the patient experienced active involvement during the previous 3 months.

From the same initial pool of 6031 patients, 500 patients were selected using a random number generator (RNG). Of these 500, 237 patients had attended our outpatient clinic during the previous 3 months and could be contacted. Among these 237, 16 (6.8%) had a first- and/or second-degree relative with BS. These were excluded from our survey. The remaining 221 patients made up the Group NF and were questioned for BS manifestations they experienced within the previous 3 months in the same manner as Group F. Also, using the same RNG, 110 random unrelated pairs were constructed among the patients in this group, who were similarly surveyed by the standard questionnaire. The study was approved by the ethical committee of Cerrahpasa Medical School and all patients gave consent to participate in the study.

Statistics

The main method of data assessment was factor analysis (FA) [11–13]. FA, a family of statistical techniques frequently used in social sciences that aim to simplify interpretation of complex sets of data, differs from statistical methods regularly used in medical research such as simple correlation and multiple regression. While these techniques mainly search for dependency of dependent variables on independent variables, FA does not make dependency assumptions.

The primary objective of FA is to simplify a complex correlation matrix consisting of many variables by reducing it to a smaller, human-interpretable one with fewer unobserved variables. These unobserved variables, or factors, are basically groups of variables that are represented individually in the initial correlation matrix. Grouping lowers the total variance of the matrix and can potentially define novel associations between variables previously thought to be unrelated. FA can be used to explore the presence of hitherto undefined clustering of signs, symptoms and laboratory anomalies in a disease state and is an exceptionally well-suited tool that can help make sense of the protean clinical manifestations of multisystem disorders of unknown aetiology, such as BS.

Before FA, data adequacy for factor extraction was ascertained by the Kaiser–Meyer–Olkin Measure of Sampling Adequacy (MSA) and Bartlett's Test of Sphericity. Clinical manifestations that occurred during the previous 3 months were included in the FA and were used to search for the symptom clusters. A patient could be in more than one cluster.

Maximum variance (varimax) rotation was applied to component matrices to make the differences between factors more pronounced. The scree plot method was used to determine the number of factors. The cut-off to report factor loadings was 0.500. Cluster frequencies and shared cluster ratios were compared using χ^2 tests.

We also performed a hierarchical cluster analysis on the clinical manifestations to examine whether they could be grouped in meaningful clusters. The tree diagrams (dendograms) of Groups F and NF show the arrangement of symptom clusters and the distance between each cluster, computed using the Euclidian distance. Statistical Package for Social Science (SPSS 16; SPSS Inc., Chicago, IL, USA) was used for both factor and cluster analysis.

Results

The percentage of BS patients who reported at least one first- and/or second-degree relative with BS was 6.3% in the total pool of 6031 registered cases and 6.8% among the 500 randomly selected patients ($P = 0.696$). All familial patients, when prospectively interviewed, confirmed that they had a first-degree relative with BS. Only two patients from the familial group also had a second-degree relative (one aunt and one uncle) with BS.

Demographic characteristics and symptom distributions of these BS patients since the beginning of their disease and during the last 3 months are summarized in Tables 1 and 2. The age, gender and disease duration of Groups F and NF were similar. While overall the symptom frequencies were, in general, similar to what we have reported in a 20-year cohort survey [14], the frequency of papulopustular lesions, uveitis and immunosuppressive use for the whole disease course (Table 1) were higher in Group NF as compared with Group F (93 *vs* 80%, 56 *vs* 44% and 69 *vs* 23%, respectively). Clinical manifestations which had a frequency of $<10\%$ since diagnosis (CNS, gastrointestinal system and pure arterial involvement) were excluded from the analyses. Oral and genital ulcers, erythema nodosum, papulopustular skin lesions, uveitis, superficial and deep vein thrombosis

Table 1 Characteristics of patients and frequency of clinical manifestations since diagnosis

Characteristic	Group F			Group NF		
	Total	Male	Female	Total	Male	Female
Number, *n*	380	217 (57)	163 (43)	221	148 (67)	73 (33)
Age, mean (S.D.), years	40 (11)	39 (11)	41 (12)	42 (9)	42 (8)	43 (9)
Disease duration, mean (S.D.), years	10 (6)	10 (6)	10 (6)	10 (4)	9 (7)	10 (5)
Oral ulcers, *n* (%)	372 (97.9)	213 (98.2)	159 (97.5)	219 (99.1)	146 (98.6)	73 (100)
Genital ulcers, *n* (%)	319 (83.9)	182 (83.9)	137 (84)	194 (87.8)	131 (88.5)	63 (86.3)
Erythema nodosum, *n* (%)	209 (55.0)	109 (50.2)	100 (61.3)	124 (56.1)	79 (53.4)	45 (61.6)
Papulopustular skin lesions[a], *n* (%)	302 (79.5)	186 (85.7)	116 (71.2)	206 (93.2)	140 (94.6)	66 (90.4)
Uveitis[b], *n* (%)	166 (43.7)	115 (53)	51 (31.3)	123 (55.7)	96 (64.9)	27 (37.0)
Joint involvement, *n* (%)	275 (72.4)	151 (69.6)	124 (76.1)	166 (75.1)	101 (68.2)	65 (89.0)
Superficial vein thrombosis, *n* (%)	39 (10.3)	32 (14.7)	7 (4.3)	30 (13.6)	24 (16.2)	6 (8.2)
Deep vein thrombosis, *n* (%)	47 (12.4)	39 (18.0)	8 (4.9)	24 (10.9)	22 (14.9)	2 (2.7)
Neurological involvement, *n* (%)	18 (4.7)	12 (5.5)	6 (3.7)	7 (3.2)	7 (4.7)	0 (0)
Gastrointestinal involvement, *n* (%)	3 (0.8)	1 (0.5)	2 (1.2)	0 (0)	0 (0)	0 (0)
Arterial involvement, *n* (%)	7 (1.8)	6 (2.8)	1 (0.6)	1 (0.5)	1 (0.7)	0 (0)
Pathergy reaction, *n* (%)	219 (55.9)	125 (63.5)	94 (59.9)	140 (63.3)	92 (62.2)	48 (65.8)
Immunosuppressive use[c], *n* (%)	89 (23.4)	62 (28.5)	27 (16.6)	153 (69.2)	105 (70.9)	48 (65.8)

[a]Group F *vs* Group NF: χ^2: 20.2, $P < 0.001$. [b]Group F *vs* Group NF: χ^2: 8.02, $P = 0.005$. [c]Group F *vs* Group NF: χ^2: 121.9, $P < 0.001$.

Table 2 Characteristics of patients and frequency of clinical manifestations during the previous 3 months

Characteristic	Group F			Group NF		
	Total	Male	Female	Total	Male	Female
Number, *n*	186	108 (58)	78 (42)	221	148 (67)	73 (33)
Age, mean (S.D.), years	38 (12)	37 (10)	41 (13)	42 (9)	42 (8)	43 (9)
Disease duration, mean (S.D.), years	9 (4)	9 (6)	9 (7)	9 (5)	9 (4)	9 (8)
Oral ulcers, *n* (%)	148 (79.6)	84 (77.8)	64 (82.1)	153 (69.2)	93 (62.8)	60 (82.2)
Genital ulcers[a], *n* (%)	35 (18.8)	20 (18.5)	15 (19.2)	61 (27.6)	38 (25.7)	23 (31.5)
Erythema nodosum[b], *n* (%)	53 (28.5)	31 (28.7)	22 (28.2)	36 (16.3)	19 (12.8)	17 (23.3)
Papulopustular skin lesions, *n* (%)	108 (58.1)	73 (67.6)	35 (44.9)	124 (56.1)	91 (61.5)	33 (45.2)
Uveitis, *n* (%)	32 (17.2)	19 (17.6)	13 (16.7)	40 (18.1)	33 (22.3)	7 (9.6)
Joint involvement[c], *n* (%)	122 (65.6)	65 (60.2)	57 (73.1)	99 (44.8)	56 (37.8)	43 (58.9)
Superficial vein thrombosis[d], *n* (%)	15 (8.1)	9 (8.3)	6 (7.7)	2 (0.9)	2 (1.4)	0 (0)
Deep vein thrombosis, *n* (%)	3 (1.6)	2 (1.9)	1 (1.3)	3 (1.4)	3 (2)	0 (0)
Neurologic involvement, *n* (%)	2 (1.1)	2 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal involvement, *n* (%)	1 (0.5)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Arterial involvement, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pathergy reaction[e], *n* (%)	95 (55.9)	56 (57.7)	39 (53.4)	140 (63.3)	92 (62.2)	25 (34.2)
Immunosuppressive use[f], *n* (%)	59 (31.7)	38 (35.2)	21 (26.9)	153 (69.2)	105 (70.9)	48 (65.8)

[a]Group F *vs* Group NF: χ^2: 4.32, $P = 0.038$. [b]Group F *vs* Group NF: χ^2: 8.8, $P = 0.003$. [c]Group F *vs* Group NF: χ^2:17.6, $P < 0.001$. [d]Group F *vs* Group NF: χ^2: 12.9, $P < 0.001$. [e]Group F *vs* Group NF: χ^2: 6.23, $P = 0.013$. [f]Group F *vs* Group NF: χ^2: 56.94, $P < 0.001$.

and joint involvement (i.e. arthritis and/or arthralgia) that occurred within the previous 3 months were the eight variables that were included.

The factorability of the original correlation matrices of eight variables was tested using Kaiser–Meyer–Olkin MSA and Bartlett's Test of Sphericity [15]. MSA values were 0.58 and 0.52 for Groups F and NF, respectively. Bartlett's Test of Sphericity was highly significant for both groups with $P < 0.001$. These showed us that the sample size was adequate and the variables were satisfactorily independent to make our data suitable for factor analysis [16].

Four factors were extracted in Group F, which explained 65% of the variation in the original matrix. In the

Table 3 Factors extracted from the rotated component matrices for Groups F and NF

	Group F					Group NF				
Factor eigenvalues	1.768	1.400	1.104	0.961		1.957	1.521	1.044	1.026	
Percentage of explained variance	22.100	17.503	13.799	12.016		24.464	19.015	13.047	12.831	
Loadings	Factor	Factor	Factor	Factor	Com	Factor	Factor	Factor	Factor	Com
Oral ulcers	**0.750**	–	-	-	0.623	-	**0.597**	-	-	0.515
Genital ulcers	-	-	**0.619**	-	0.598	-	**0.719**	-	-	0.619
Erythema nodosum	-	-	**0.829**	-	0.705	-	**0.681**	-	-	0.571
Papulopustular skin lesions	**0.553**	-	-	-	0.575	-	-	**0.782**	-	0.677
Uveitis	-	-	-	**0.808**	0.663	-	-	-	**0.884**	0.784
Joint involvement	**0.775**	-	-	-	0.631	-	-	**0.665**	-	0.599
Superficial vein thrombosis	-	**0.748**	-	-	0.687	**0.950**	-	-	-	0.906
Deep vein thrombosis	-	**0.816**	-	-	0.751	**0.930**	-	-	-	0.876

Values in bold type are variables that made up individual factors. Com: communalities.

order of decreasing eigenvalue (in parenthesis), these factors were: Factor 1 (1.768), the association between oral ulcers, papulopustular skin lesions and joint involvement; Factor 2 (1.400), the association between superficial and deep vein thrombosis; Factor 3 (1.104), the association between genital ulcers and erythema nodosum; and Factor 4 (0.906), uveitis alone.

Four factors were extracted in Group NF, which explained 69% of the variation in the original matrix. In order of decreasing eigenvalue (in parenthesis), these factors were: Factor 1 (1.957), the association between superficial and deep vein thrombosis; Factor 2 (1.521), the association between oral ulcers, genital ulcers and erythema nodosum; Factor 3 (1.044), the association between papulopustular skin lesions and joint involvement; and Factor 4 (1.026), uveitis alone. Factors, eigenvalues, communalities and relative contribution of each factor to the total variance of the original matrices are outlined in Table 3. The cluster analysis showed very similar symptom clusters (see Figs 1 and 2).

Of the factors we extracted from either group, only symptom clusters containing the papulopustular skin lesions and joint involvement association had a significantly higher frequency in Group F. In Group F, oral ulcers also clustered with papulopustular skin lesions and joint involvement. When we compared the number of patients with oral ulcers, papulopustular skin lesions and joint involvement in Groups F and NF, the frequency was significantly higher among the Group F (39.2 *vs* 21.5%, $P < 0.001$). Similarly, the number of patients with papulopustular skin lesions and joint involvement was significantly higher in Group F as compared with NF (41.9 *vs* 29%, $P = 0.006$). Comparisons of symptom cluster frequencies for Groups F and NF are outlined in Table 4.

Furthermore, the papulopustular skin lesion and joint involvement association was concomitantly present in 5 of the 17 related pairs identified in Group F, whereas this association was shared by only 5 of the 110 unrelated pairs of randomly matched patients from Group NF [29.0 *vs* 4.5%, $P = 0.004$, risk ratio (RR) = 6.47, 95% CI 2.15, 18.89].

Discussion

There were two main outcomes to this study: (i) We have re-confirmed the presence of separate symptom clusters in our large population of BS patients. The attributes of these clusters were also similar to what we had previously described [6–7]. (ii) One of these clusters, the papulopustular lesion–arthritis cluster, was significantly more prevalent among the familial cases as evidenced by the significantly increased frequency of the same cluster among (a) the patients in Group F as compared with those in Group NF and (b) among the familial as compared with the randomly generated unrelated patient pairs.

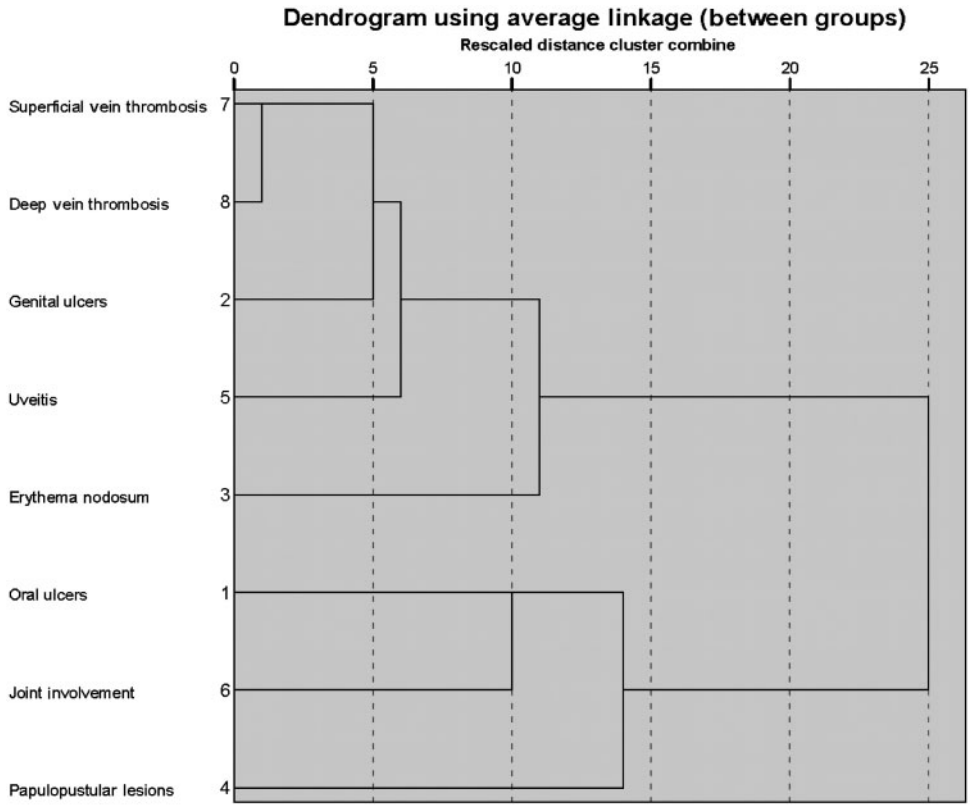
One study from Israel and another more recent study from Greece also looked at such clustering of symptoms in BS [17–18]. The clusters we described were not observed. However, there are substantial methodological differences between these studies and the previous and current surveys from our centre. The Israeli and Greek studies were retrospective and based on patient charts, while the Israeli survey also included paediatric patients. On the other hand, our three surveys (the initial paper being only on the association of papulopustular lesions and arthritis), including the current work, were prospective, in the sense that the patients were questioned by a standard questionnaire at the time of the survey. Furthermore, they included only adult patients. The number of patients in the retrospective studies was also considerably less when compared with our reports. The Greek study also used a slightly different methodology. They performed χ^2 tests to compare subgroups of patients with or without each manifestation. They had not identified any associations with this method. Further, they used FA (only in their discussion) to analyse their data and they observed four clusters: (i) oral ulcers, joint involvement, thrombophlebitis; (ii) genital ulcers, erythema nodosum, folliculitis; (iii) CNS involvement, intestinal involvement; and (iv) uveitis. There is also the possibility that the differences observed could represent real geographical differences in disease expression, as has already been suggested not only in reference to what is being discussed, but also to what has been observed in

Table 4 Comparison of frequencies of symptom clusters in Groups F and NF

Symptom cluster	Factor	Group F, %	Group NF, %	*P*
Symptom clusters (extracted from group F)				
Oral ulcers + papulopustular lesions + joint involvement	1	73 (39.2)	48 (21.5)	0.000
Deep vein thrombosis + superficial vein thrombosis	2	2 (1.1)	2 (0.9)	0.862
Erythema nodosum + genital ulcers	3	17 (9.1)	16 (7.2)	0.484
Uveitis	4	32 (17.2)	40 (18.1)	0.814
Symptom clusters (extracted from group NF)				
Deep vein thrombosis + superficial vein thrombosis	1	2 (1.1)	2 (0.9)	0.862
Erythema nodosum + genital ulcers + oral ulcers	2	16 (8.6)	15 (6.8)	0.492
Joint involvement + papulopustular skin lesions	3	78 (41.9)	64 (29.0)	0.006
Uveitis	4	32 (17.2)	40 (18.1)	0.814

P-values calculated using χ^2 and Fisher's exact tests. Fisher's exact test was used when the number of cases was fewer than five for any given symptom cluster. $P < 0.05$ denotes statistical significance.

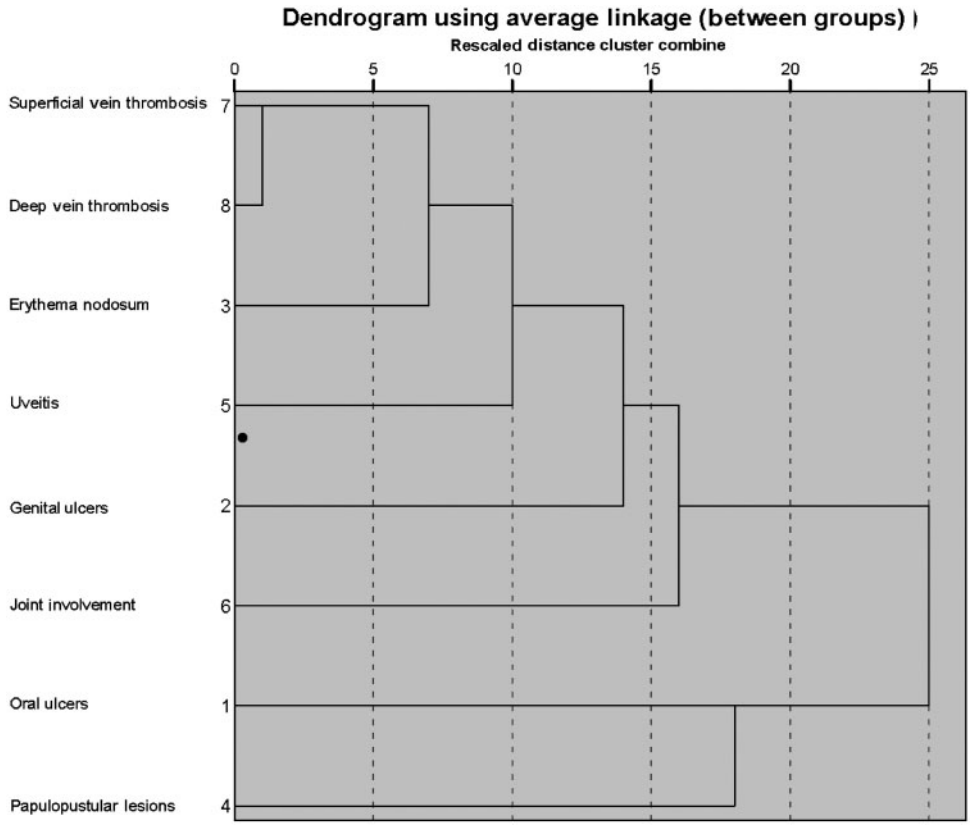
Fig. 1 Dendogram showing clustering of clinical manifestations in familial BS patients (Group F).



the differing frequencies of gastrointestinal disease and pathergy in patients from different parts of the world [19]. Most of the data regarding geographical differences in disease expression of BS come from observational reports of cohorts from different countries. However, these cohorts are formed with several biases, including differences in referral systems and differences in the clinics they are reported from, such as ophthalmology and dermatology. Studies comparing disease phenotypes in different geographies using standardized methods for patient recruitment are needed to better address this issue.

Unlike similar previous studies, we chose to include BS manifestations that occurred in a relatively narrow time frame, namely 3 months. We hypothesized that disease manifestations that share pathogenetic mechanisms would tend to occur closer in time. Also, one would

FIG. 2 Dendogram showing clustering of clinical manifestations in non-familial BS patients (Group NF).



expect while seeking a relationship between a wide array of different manifestations in a relatively sizeable matrix that inclusion of data accumulated since diagnosis would likely weaken the factorability of the matrix and potentially obscure relationships between disease manifestations that may actually exist. Moreover, limiting the symptoms to those that occurred during the previous 3 months would be less prone to recall bias.

Our study had a number of limitations. FA is more commonly applied to linear rather than to binary data [20]. The reason we used FA here was that this statistical tool was instrumental in bringing up the acne–arthritis cluster in BS in a previous study [7], an association, in turn, that had already been suggested in a still earlier study, again from our unit, that time utilizing a different methodology [6]. Furthermore, in the current work we observed almost identical symptom clusters. A second issue is that disease manifestation data pertaining to the preceding 3 months was obtained with a phone interview for 72.6% of the familial group, whereas 100% of the non-familial patients were interviewed at our clinic. There are two main reasons for this difference. Our dedicated multidisciplinary Behçet's Syndrome Research Center at Istanbul University serves as a referral centre for a diverse population from all across Turkey and abroad. As explained in the 'Methods' section, we identified the familial cases from a pool of 6031 registered patients. Many of these identified familial patients reside outside Istanbul, making it logistically very difficult for them to come in for a face-to-face interview. The non-familial cases, on the other hand, were those who were able to attend the clinic within the past 3 months, among a randomly selected subset of patients. The disparity in uveitis and immunosuppressive use percentages between the two groups may also be related to this difference, the group receiving more active treatment being followed more closely. It might also be reasoned that Group NF receiving more immunosuppressives would tend to have less arthritis and papulopustular lesions due to disease suppression, generally with more drug use. The frequency of papulopustular lesions was similar while the frequency of arthritis for the whole group was indeed less ($\chi^2 = 16.8$, $P < 0.0001$) among Group NF, as seen in Table 2. On the other hand, this sort of bias, if operative, would similarly and preferentially decrease the frequency of other disease clusters in Group NF as well. As seen in Table 4, this was not the case. It was also interesting to note that other clusters of disease expression, such as dural sinus thrombi and deep vein thrombosis, did not show familial clustering [21]. This we take as further evidence for the presence of different pathogenetic pathways in BS.

We do not have information on the HLA-B51 status of these patients. It would be interesting to formally compare the frequency of HLA-B51 in BS patients who have papulopustular lesions and arthritis with patients who have other manifestations. On the other hand, up to now the only consistent association that could be shown was between HLA-B51 and eye involvement [22–24].

Our previous studies on pustular lesions and their association with joint involvement in BS have shown that the pustular lesions of BS are not sterile [25], enthesopathy can also accompany this association [8], and HLA-B27 positivity and sacroiliitis are infrequent among these patients [26]. Our observations suggest that the association of pustular lesions and joint involvement in BS is quite similar to acne-associated ReA. A distinct pathogenetic mechanism, possibly involving hypersensitivity to certain microorganisms, may be underlying this association. Our current findings of significantly increased frequency of this cluster in familial BS patients and its being more frequently shared by family members suggest that the mechanism underlying this phenotypic cluster also might have a heritable component. Thus it may be hypothesized that the presence and persistence of certain microorganisms in genetically susceptible BS patients may be responsible for this association.

Familial clustering of certain features in other rheumatological conditions has previously been described. Familial JRA patients have concordance for tenosynovitis, seropositivity, pauciarticular and polyarticular disease onset, but not systemic disease onset [27]. Similarly, sibling risk ratios were increased for thrombocytopenia, discoid rash, neurological involvement and haemolytic anaemia in lupus patients and seropositivity, nodules and age at diagnosis showed familial clustering among RA patients [28–29]. These observations all point to the complex aetiologies underlying diverse inflammatory diseases/syndromes including BS [30].

Rheumatology key messages

- The previously described papulopustular lesions/arthritis cluster in BS also clusters in familial cases.
- Different pathogenetic pathways may result in separate phenotype clusters in BS.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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