Target Organ Associations in Turkish Patients with Behçet's Disease: A Cross Sectional Study by Exploratory Factor Analysis

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ABSTRACT. ***Objective.*** To look for target organ associations in Turkish patients with Behçet's disease (BD).

Methods. We studied target organ associations in 272 consecutive patients with BD. The occurrence of any of the clinical manifestations related to BD within the previous 3 months was sought by history questionnaire completed by a rheumatologist and by physical examination. Factor analysis was used to analyze the data.

Results. Four factors were identified by factor analysis of variables oral and genital ulcers, erythema nodosum, papulopustular skin lesions, uveitis, superficial and deep vein thrombosis, joint, arterial, neurological, and gastrointestinal involvement; the 4 identified factors explained 69% of the original information of the matrix. There was an association between oral ulcers, genital ulcers, and erythema nodosum (Factor 1); and between superficial and deep vein thrombosis (Factor 2). Uveitis was identified as a distinct feature, and was negatively associated with erythema nodosum (Factor 3) only among the females. There was also an association between papulopustular skin lesions and joint involvement (Factor 4). Factors 2 and 3 had higher scores in males ($p = 0.001$ and $p = 0.009$, respectively) versus females.

Conclusion. We studied clinical features of BD in Turkish patients. The 4 factors we identified by factor analysis differ from a previous study from Israel, probably due to different methodologies used in the 2 studies. One factor described in our study, the association between papulopustular lesions and arthritis, supports findings of our recent study. A recognized association between superficial and deep vein thrombosis was also confirmed. (J Rheumatol 2002;29:2393–6)

Key Indexing Terms:
BEHÇET'S SYNDROME TARGET ORGAN ASSOCIATION FACTOR ANALYSIS

Behçet's disease (BD) is a vasculitis characterized by oral and genital ulcers and uveitis. After its first description by Hulusi Behçet, additional target organ involvement, including neurologic, gastrointestinal (GI), pulmonary arterial, venous and peripheral arterial disease, has been recognized and added to the disease spectrum.

Not only are the clinical findings of BD diverse, but there are also important differences in disease expression between different regions. BD is strongly associated with HLA-B51 antigen in Mediterranean countries and in Japan, but this association becomes less important in North America and in Europe[1-3]. While the pathergy reaction has diagnostic importance in Turkey and Japan, this reaction is rarely seen in English patients[4,5]. Although reported in only 5% of patients with BD in a prospective study from Turkey, neurologic involvement may be more prevalent in European and American patients[6,7]. In contrast to the Japanese, symptomatic GI involvement is rarely seen among the Turkish patients[8].

The pathogenesis of BD is not clear. Both viral and bacterial agents have been implicated and there are some immunologic aberrations. However, none leads to a unifying pathogenic mechanism[9,10].

The common dependence techniques of statistics, like simple correlation or multiple regression, assume independent and dependent variables in analyzing data. These tools take an independent (criterion or predictor) variable(s) and search for the dependency of other, dependent variable(s) on this independent variable. Factor analysis, on the other hand, assumes no such dependency[11]. The main aim of factor analysis is to express the multiple variables that make up a correlation matrix by a lesser number of hitherto unobserved quantities called factors. In doing so a factor analysis also lowers the total variance of the matrix, which is the simple sum of the original number of variables that make it up. In the case of a disease of many clinical and/or laboratory findings, each representing a variable, factor analysis may help define yet unidentified, underlying factor(s) that would group some of these variables together. This grouping, in

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turn, might have pathogenic implications. Thus a factor analysis is particularly suitable to look at and perhaps make sense of the various and differing clinical manifestations of a multisystem disease of unknown etiology, like BD.

We studied a group of Turkish patients with BD using factor analysis.

MATERIALS AND METHODS

Two hundred seventy-two consecutive patients with BD were recruited into the study; all were attending the dedicated, multidisciplinary Behçet's Syndrome Research Centre Outpatients Clinic at the Cerrahpasa Medical Faculty at the University of Istanbul in Turkey, which has about 4500 registered patients. In each patient the diagnosis of BD had been established. All patients fulfilled the International Study Group for BD classification criteria[12]. After physical examination we asked all patients about any clinical manifestations related to BD experienced within the previous 3 months and recorded their responses on a questionnaire form. The same physician, a rheumatologist, filled in all questionnaires; no patient refused to participate. All patients were also routinely seen by a dermatologist and by an ophthalmologist regarding any ocular symptoms.

After coding, the data were entered onto a computer database. The Statistical Package for Social Science software was used for the factor analysis (see Appendix for selected definitions). To search for target organ associations, the variables oral and genital ulcers, erythema nodosum, papulopustular skin lesions, uveitis, superficial and deep vein thrombosis, and joint involvement (i.e., arthritis and/or arthralgia) were chosen. Clinical manifestations that had a frequency of < 10% (central nervous system, GI, and pure arterial involvement with frequencies of 3%, 1%, and 1%, respectively) were excluded from analysis.

In order to make the differences between factors more pronounced a maximum variance (varimax) rotation was applied[13]. We used "eigenvalue over one criterion" for the number of factors. Statistical comparisons were made by the chi-square test. The results were also analyzed according to gender (data not given).

RESULTS

Demographic characteristics and the frequency of the clinical manifestations of the patients are shown in Table 1. Oral ulceration, erythema nodosum, and arthralgia were more frequent among the female patients while the reverse was true for the superficial and the deep vein thrombophlebitis. Ninety-five patients (86 male) were using immunosuppressive drugs (azathioprine and/or cyclosporine).

Factor analysis revealed 4 factors that explained 69% of the original information on the matrix as follows: Factor 1 represented the association between oral and genital ulcers as well as with erythema nodosum; Factor 2, the association between superficial and deep vein thrombosis; Factor 3, uveitis by itself; and Factor 4, the association between papulopustular skin lesions and joint involvement. The eigenvalues of the 4 factors were 1.983, 1.467, 1.096, and 1.008, in decreasing order, i.e., the highest contribution to the overall variance in the matrix came from the togetherness of the 3 clinical manifestations that made up Factor 1. Factors, their relative contributions to the total variance and the communalities for each of the variables are shown in Table 2.

The measure of sampling adequacy (MSA) was 59% for the correlation matrix of the 8 clinical variables. In addition MSA was greater than 50% for all variables except uveitis, for which it was 41%. When the data were separately analyzed for males and females (data not shown), the results of the analyses did not change appreciably. The important items to note were that Factor 2 and 3 had significantly higher scores among the males ($p = 0.001$ and $p = 0.009$, respectively) and Factor 3 was modified among the females by the addition of erythema nodosum to the uveitis as a negative association.

DISCUSSION

Our factor analysis identified 4 independent factors that explained 69% of the original information of the entire matrix of diverse clinical findings (variables) of a group of BD patients from Turkey. As expected, mucocutaneous manifestations of oral and genital ulcers as well as erythema nodosum (Factor 1) tended to occur together. The associa-

Table 1. Characteristics of patients and frequency of clinical manifestations during the 3 month period.

	Total (%)	Male (%)	Female (%)	P
Number	272	153 (56)	119 (44)	
Mean age ± SD, yrs	35 ± 9	34 ± 9	36 ± 10	NS
Oral ulcers	177 (65)	83 (54)	94 (79)	0.001
Genital ulcers	62 (23)	34 (22)	28 (24)	NS
Erythema nodosum	53 (19)	17 (11)	36 (30)	0.001
Papulopustular skin lesions	125 (46)	70 (46)	55 (46)	NS
Uveitis	52 (19)	34 (22)	18 (15)	NS
Arthritis	27 (10)	12 (8)	15 (13)	NS
Arthralgia	88 (32)	36 (24)	52 (44)	0.001
Superficial vein thrombosis	45 (17)	35 (23)	10 (8)	0.001
Deep vein thrombosis	32 (12)	28 (18)	4 (3)	0.001
Neurologic involvement	9 (3)	7 (5)	2 (2)	NS
GI involvement	3 (1)	3 (1)	0 (0)	NS
Arterial involvement	2 (1)	2 (1)	0(0)	NS
Immunosuppressive drug use*	95 (35)	95 (35)	95 (35)	0.001

* Azathioprine and/or cyclosporine. NS: not significant.

Table 2. Factors derived from the rotated varimax.

Factor Eigenvalues	1.983	1.467	1.096	1.008	
Percentage of explained variance	24.79	18.34	13.71	12.60	
Loadings	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Communalities**
Oral ulcers	**0.608**	–0.088	0.057	0.471	0.603
Genital ulcers	**0.790**	0.024	–0.236	–0.022	0.680
Erythema nodosum	**0.656**	0.317	0.160	0.269	0.629
Papulopustular skin lesions	0.311	–0.163	–0.361	**0.629**	0.649
Joint involvement	–0.028	0.014	0.153	**0.863**	0.769
Uveitis	–0.035	0.009	**–0.919**	–0.026	0.846
Superficial vein thrombosis	–0.025	**0.866**	0.008	0.045	0.752
Deep vein thrombosis	0.011	**0.853**	–0.010	–0.088	0.735

Values in bold face: variables that made up individual factors.

tion between superficial and deep vein thrombosis we observed (Factor 2) has also been reported by Koc, *et al* from Ankara, Turkey[14]. Thus it is conceivable that superficial and deep vein thromboses are pathogenically related. In contrast to the results of our study Koc, *et al* reported a positive association between uveitis and vascular involvement[14]. In Koc's study, however, uveitis was less frequent (36%) than in our report and/or as usually seen in our dedicated clinic[15]. Different patient referral patterns might be one reason for this discrepancy.

Uveitis in BD (Factor 3) has enough distinguishing features to stand by itself as a representative feature. Therefore all patients with uveitis should carefully be searched for other stigmata of BD.

Studying a different group of patients, our group recently reported that acne-like lesions were indeed more prevalent in BD patients with arthritis compared to those without[16]. Likewise, in this study, Factor 4 represented the association between papulopustular skin lesions and joint involvement. This raises the possibility for consideration that the arthritis of BD might be related to acne-associated arthritis.

In the only previous factor analysis study in BD, Krause, *et al*[17] defined 5 factors. Factor 1 was the association between folliculitis and genital ulcers, which were inversely correlated with uveitis. Factor 2 was the association between papulopustular skin lesions and GI symptoms. Factor 3 was the inverse association between superficial vein thrombosis and erythema nodosum. Factor 4 was the association between deep vein thrombosis and neurologic involvement and Factor 5 was joint disease.

It is to be noted that the 4 factors that emerged from our current study were different from those Krause, *et al* reported from Israel[17]. Up to now no formal analyses have looked at the different disease patterns between Israeli and Turkish patients. However, in comparing the clinical findings reported in Krause's paper and in ours, we see some important differences, most notably that arthritis is observed in around 50% of our patients compared to 81% reported in Krause, *et al*; and GI involvement (a component of a factor in the Krause, *et al* report) was distinctly rare among our patients[8]. Also a good 19% of the patients in the Israeli series had GI disease.

There are some methodological differences that might also explain the different results found. The current study only took into account those clinical findings that occurred together within a short time span of 3 months. We had reasoned that the clinical associations we thus described would perhaps be pathogenically more closely related since they occurred close together in time. The Krause, *et al* work on the other hand, included data on all recorded disease manifestations in any one patient at any time. This was also one of the main reasons we had chosen a 3 month time window for study. The other reason was a possible recall bias that might potentially influence our findings.

Our study was conducted only among the adult patients whereas pediatric patients constituted 43% of the 68 patients of the Krause, *et al* work. Children with BD, on the other hand, usually have a somewhat different clinical presentation when compared to adult patients. In general they have less frequent uveitis and genital ulceration but more frequent neurologic involvement[18]. Krause, *et al*[17] in fact mention that the frequency of 2 of the factors they described differed between pediatric and the adult cases.

Finally, in contrast to our current study, which reports the experience of a single center, the Krause, *et al* work reported a multicenter experience; it is thus conceivable that not only the patient referral patterns but also the clinical interpretation of some findings might have differed between the centers. This is particularly important in interpreting the biological meaning of Factor 3 in the Krause study, the inverse relation between superficial vein thrombosis and erythema nodosum. The lesions are both nodular skin lesions, and it is usually quite difficult clinically to tell one from the other[15]. Thus it is conceivable that a diagnosis of one would categorically exclude the other, leading to the inverse association described.

Our study had some limitations. Having a 59% MSA for our entire matrix (55% in the Krause study) may raise the issue of the appropriateness of factor analysis in our sample, since a factor analysis MSA value below 0.50 is considered

unacceptable. When we applied factor analysis to 237 patients in our group who had at least one clinical manifestation of BD at the time of evaluation, the MSA value for the entire group was raised to 63%, without any change in the 4 factors that our analysis defined at the end (data not given). Furthermore another test of appropriateness, the Bartlett test of sphericity, was highly significant with a value of 280.0 ($p = 0.0001$).

The 3 month time window of our study might have led to underreporting of clinical manifestations that might have enhanced our results. This is particularly true for relatively rare complications like arterial vascular disease. The second point to consider is that, even though the time span was relatively short at 3 months, our data collection still depended on recall. Finally, many of our patients were using potent drugs to suppress disease manifestations (Table 1) and this could also have obscured some biologically important organ involvement associations.

We set a 10% frequency lower limit for the clinical manifestations that were going to be included in our factor analysis. This was an attempt to put more robustness into our data. It turned out that 3 manifestations (central nervous system, GI, and arterial disease) all had frequencies equal to or less than 3% for the 3 month time window chosen for our study. Thus we do not think the inclusion of these 3 clinical findings would have yielded more useful information in the particular data set we analyzed.

We were gratified to see that one of the associations highlighted in this study, that between papulopustular lesions and arthritis (Factor 4), was in accord with another blind controlled study from our group, specifically designed to look at this association[16]. The association and the confirmatory data about the association of superficial and deep vein thrombosis (Factor 2) might be important leads in further studies on the unknown pathogenesis of BD.

In summary, factor analysis, although yielding rather different results in the initial 2 instances where it was applied to BD, seems to be a fruitful way to look at target organ associations in this syndrome of diverse and geographically different manifestations. Further, prospective studies, with special attention to patient referral patterns and data collection methods, are desirable.

APPENDIX.

Selected definitions related to factor analysis.

Loading value: The relative contribution of each variable to the factors that emerge from a factor analysis.

Communality: The amount of variance within each variable that is explained by the factors in common with all other variables. Numerically it is the sum of all the squared loadings.

Eigenvalue (principal value): A measure of the relative contribution of an individual factor to the total variance (information). The sum of eigenvalues is equal to the number of original variables.

Measure of sampling adequacy (MSA): An index for the appropriateness of factor analysis that ranges from 0–1 with values below 0.50 indicating unacceptability.

The Bartlett test of sphericity: A test measuring the statistical probability that at least some of the variables in a correlation matrix have significant correlations.

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