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BRIEF PAPER

Disease patterns of patients with Behçet's disease demonstrated by factor analysis

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ABSTRACT

Objective

To explore the main patterns of Behçet's disease (BD) expression, applying factor analysis.

Methods

Sixty-eight BD patients were studied. The following disease manifestations were used for the factor analysis: genital ulcerations, typical skin lesions (erythema nodosum, folliculitis or papulo-pustular rash), uveitis, CNS involvement, joint disease, deep vein and superficial vein thrombosis, and gastrointestinal manifestations. The results were further analyzed according to sex, HLA typing, and childhood vs. adult-onset disease.

Results

Five factors were derived, which accounted for 69% of the variance of the matrix. Factor 1 represented the association between folliculitis and genital ulceration. Factor 2 represented the association between papulo-pustular rash and gastrointestinal symptoms. Factor 3 represented the inverse association between superficial vein thrombosis and erythema nodosum. Factor 4 represented the correlation between deep vein thrombosis and neuro-Behçet. Factor 5 represented joint disease.
No difference was found between males and females in relation to factors 1, 2 or 5, but factors 3 and 4 had higher scores in male patients ($p = 0.1$ and $p = 0.07$, respectively). Factor 3 was significantly higher in patients with HLA-B5, compared to HLA-B5-negative BD patients ($p < 0.001$). Factors 1 and 3 were higher in patients with adult onset of the disease ($p = 0.07$, and $p = 0.003$, respectively), while factor 2 was higher in patients with childhood-onset BD ($p = 0.07$).

Conclusions

The application of factor analysis revealed possible associations between distinct types of skin lesions, or venous thrombosis, and other disease manifestations of Behçet's syndrome, some of which were sex, age at onset, or HLA-related.

Introduction

Traditionally described as a triad consisting of recurrent aphthous stomatitis, genital ulcerations, and ocular disease, Behçet's disease (BD) is now recognized as a multisystem disorder, the clinical expression of which may be dominated by mucocutaneous, articular, neurologic, urogenital, vascular, intestinal or pulmonary manifestations (1, 2).

It is well known that BD has a diverse clinical expression in various geographical areas (3), such as the pathergy reaction which is highly sensitive and specific in BD patients from Turkey and Japan but usually negative in British patients (4), or gastrointestinal involvement which occurs in about one-third of patients from Japan but rarely in Mediterranean countries. O'Neill *et al.* (5) described regional differences in several of the clinical manifestations of BD. They found that BD patients in Middle Eastern countries and the Mediterranean basin generally have less widespread disease when compared with patients from Western countries (the UK and USA), as manifested by lesser rates of arthritis, vascular problems and CNS abnormalities. Similarly, Kone-Paut *et al*. (6) found more neurological and gastrointestinal complications among patients from France and Saudi Arabia, whereas patients from Turkey had more frequent cutaneous manifestations. Nevertheless, Davies *et al*., who compared the expression of BD between a group of 19 British patients and a group of 49 Turkish patients using cluster analysis, found no difference in their clinical manifestations apart from the pathergy reaction (4).

Despite the reported heterogeneity in the clinical presentation of BD, the inter-relationship between the various manifestations of the disease has not yet been studied, and may have been overlooked due to the numerous possible combinations of clinical manifestations. Awareness of these combinations, or disease patterns, might give us a better understanding of the disease.

To further address these issues, we evaluated the principle associations between various clinical manifestations in Israelian BD patients, applying factor analysis. Factor analysis is a multi-variate technique which reduces a matrix of cor-

relations to a few factors, while retaining as much information as possible from the original matrix. The factors represent the main patterns of correlations among the variables, defined by the relative donation of the variables to each factor (7).

Patients and methods

Patients with BD from several medical centers in Israel were studied. The patients were recruited by an expert rheumatologist from various medical centers, including specialized clinics (rheumatologic, neurologic, dermatologic, vascular and eye clinics) and internal medicine and pediatrics departments. All patients who fulfilled the International Study Group criteria for BD (8) were included in the study. Data from medical files and patient interviews with respect to the various manifestations of the disease, the mode and the age of disease presentation were collected. Most patients had been followed sequentially for several years, while some others had been referred for consultation and were interviewed only once. The data used for the analysis was comprised of the summation of all the manifestations which ever occurred for a given patient.

Statistical analysis

For the factor analysis we included both major and minor disease manifestations: genital ulcerations, typical skin lesions (erythema nodosum, folliculitis or papulopustular rash), uveitis, CNS involvement, joint disease, deep or superficial vein thrombosis, and gastrointestinal manifestations (GI). Oral ulcers were not included, since by definition they were present in all patients. Pathergy test data was available for only 37 out of 68 patients, and hence was not included in our calculations. Clinical manifestations with a very low rate of occurrence (less than 10%) were also not included. All manifestations were encoded as "1" for present, and "0" for absent.

To perform the principal component analysis on the correlation matrix of clinical manifestations, we used the FACTOR procedure of the Statistical Analysis System (SAS Institute, USA). The sampling adequacy (i.e., if there is an adequate correlation for factor analysis between a specific variable to the other variables) was tested both for the matrix and for each variable using Kaiser's measure (9). The most explanatory factor matrix was obtained by use of an orthagonal rotation (varimax).

The factors were further compared between classes (sex, disease onset before or after age 16 years, and HLA typing) using Student's t-test.

Linear correlation between each of the factors and the disease duration was tested by the standard Pearson moment correlation method.

Results

Sixty-eight BD patients were studied, 30 males (44.1%) and 38 females (55.9%). Thirty-nine patients (57.4%) had adult-onset disease, and 29 patients (42.6%) had childhood-onset disease (i.e., before the age of 16 years). The mean age was 33.7 ± 15.6 (range 7 - 67) years, the mean disease duration (the time interval between the age at disease onset and the age at the last visit of the patient to the clinic) was 13.0 ± 8.6 years. The clinical characteristics of the patients are presented in Table I.

For the correlation matrix of the 10 clinical manifestations, Kaiser's measure of sampling adequacy was 0.55, and for each of the variables it was ≥ 0.5 (except for joint disease, where it was 0.36). Five factors were derived, which accounted for 69% of the variance of the matrix. The final communality estimate for each manifestation (which represents the proportion of variance in the variable explained by all the factors) was ≥ 60%.

Table I. Clinical characteristics of 68 BD patients throughout their disease course.

	No.	%
Males	30	44.1
Females	38	55.9
Oral ulcers	68	100
Genital ulcers	48	70.6
Uveitis	32	47.1
Erythema nodosum	23	33.8
Folliculitis	31	45.6
Papulopustular rash	10	14.7
Positive pathergy test	18/37	48.6
Joint disease	55	80.9
Deep vein thrombosis	11	16.2
Superficial vein thrombosis	11	16.2
Chronic gastrointest. complaints	13	19.1
Neuro-Behçet's	10	14.7
Arterial involvement	2	2.9
Pleuropulmonary manifestations	6	8.8

The factor pattern obtained by varimax rotation is shown in Table II. Factor 1 (which explained 19% of the variance of the original matrix) represented the association between folliculitis (loading of 0.735) and genital ulceration (loading of 0.675), which were inversely correlated with the presence of uveitis (-0.765). Factor 2 (16% of variance) represented the association between papulopustular rash (loading of 0.761) and gastrointestinal symptoms (0.740). The GI symptoms in our patients were all mild, manifesting as chronic abdominal

Table II. Pattern matrix: Factor loadings for the clinical variables and the percentage of the total variance attributed to each factor.

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Foliculitis	0.735*	0.051	-0.030	0.040	0.236
Papulo-pustular	-0.090	0.761*	-0.091	-0.133	-0.156
Erythema nodosum	-0.189	-0.388	-0.624*	0.242	0.364
Genitalia	0.675*	-0.161	0.266	0.032	-0.138
Ocular	-0.765*	-0.106	0.165	0.176	0.147
Gastrointestinal	0.089	0.740*	0.027	0.143	0.236
Joints	-0.007	0.048	0.074	-0.070	0.873*
Superficial vein thrombosis	-0.086	-0.158	0.804*	0.152	0.207
Deep vein thrombosis	0.158	-0.148	0.298	0.766*	0.032
Central nervous system	-0.293	0.158	-0.244	0.720*	-0.116
% of variance	19	16	12	11	11

*Variables with high loading.

pain or diarrhea with no GI bleeding or bowel perforation. Factor 3 (12% of the variance) represented the inverse association between superficial vein thrombosis (loading of 0.804) and erythema nodosum (-0.624). Factor 4 (11% of the variance) represented the correlation between deep vein thrombosis (loading of 0.766) and neuro-Behçet (loading of 0.720). The subgroup of patients with neuro-Behçet included 2 patients with brain stem syndrome, 3 with meningoencephalitis, 4 with pseudotumor cerebri, and one with subarachnoid hemorrhage. Factor 5 (11% of variance) represented joint disease (loading of 0.873).

The results were further analyzed in relation to the age at disease-onset, sex and HLA typing. No difference was found between males and females in relation to factors 1, 2 or 5, but factors 3 and 4 (inverse relation between superficial vein thrombosis and erythema nodosum, and the association between DVT and neuro-Behçet) were higher in male patients ($p = 0.1$ and $p = 0.07$, respectively). In relation to HLA-B5, we found a significantly higher score for factor 3 in patients with HLA-B5, compared to the HLA-B5-negative BD patients ($p < 0.001$). Factors 1 and 3 were higher in patients with adult-onset BD (i.e. after the age of 16 years) ($p = 0.07$ and $p = 0.003$, respectively), while factor 2 had a higher score in patients with childhood-onset disease ($p = 0.07$). There was no linear correlation between any of the 5 factors and the disease duration.

Factors 1 and 3, which contained inverse correlations, were further explored by conducting factor analysis in subgroups of mutually exclusive variables, i.e. the age at onset, sex and HLA typing. The same negative correlations were found in each of the subgroups (data not shown).

Discussion

We applied factor analysis to the clinical variables of patients with Behçet's disease in order to explore the main patterns of disease expression. Five factors were extracted, which essentially represented an association between distinct types of skin lesions, or venous thrombosis, and other disease manifestations. Those factors explained 69% of the variance of the original matrix. Factors 1 and 2 represented a close association between folliculitis and genital ulcerations, and between papulopustular rash and minor gastrointestinal symptoms. Such associations have not yet been reported, possibly because of the great number of clinical variables in BD and therefore the numerous possible combinations in a given patient, making it difficult to recognize specific patterns of disease expression. It is also possible that these correlations might represent a distinct expression of the disease in our area, since it has been reported that BD may have different clinical expressions in various geographical areas (3-6). The lower prevalence of factor 1 and the higher prevalence of factor 2 in patients with childhood-onset BD, is probably associated with the higher rate of GI symptoms and the lower rate of genital ulcerations in childhood BD in our area (10). The pathophysiological significance of these associations remains to be determined.

Factor 3 demonstrated an inverse correlation between superficial venous thrombosis and erythema nodosum, which was more common in male patients. The inverse correlation of these manifestations can partly be explained by the tendency of vascular complications in BD to affect male patients, as reported by Koc *et al.* (11). In contrast, erythema nodosum has a clear predilection for female patients (1, 3). The inverse correlation between superficial thrombophlebitis and erythema nodosum might have also resulted from an improper distinction between erythema nodosum and superficial vein thrombosis. It has been reported that superficial vein thrombosis in BD, which presents as soft-tissue swelling, redness and tenderness, might be confused with erythema nodosum (3, 12). Factor 3 was significantly higher in HLA B5-positive patients ($p < 0.001$). Previous studies on the possible correlation between HLA-B5 and different clinical manifestations of BD have yielded conflicting results. Muftuoglu *et al.* (13) found no association between HLA-B5 and the age at disease onset, or the incidence of occular disease, arthritis, thrombophlebitis or erythema nodosum. Azizleri *et al.* (14) reported a higher incidence of HLA-B5 in patients with genital ulcers, and a lower incidence in patients with thrombophlebitis. Our study is the first to point to a possible correlation of HLA-B5 with superficial, but not deep, thrombophlebitis. Surprisingly, no association was found between superficial and deep vein thrombosis, in contrast to the study of Koc *et al.* (11) who reported superficial thrombophlebitis as a risk factor for major vein occlusion. Our results, however, are in line with a recent study in which the occurrence of superficial and deep vein thrombosis in the general population was found to be unassociated (15). The results of our study suggest that superficial and deep vein thrombosis might involve different pathogenic mechanisms in BD.

Of interest is the association between peripheral deep vein thrombosis and neuro-Behçet revealed by factor 4. Central nervous system (CNS) involvement is one of the most serious complications in BD. The neurological manifestations of neuro-Behçet include brain stem syndrome, cranial nerve palsies, corticospinal tract disease, meningoencephalitis, seizures, subarachnoid hemorrhage and pseudotumor cerebri (1-3, 16). The etiopathogenesis of neuro-Behçet is as yet unknown, but intracranial vascular disease in the form of cerebral venous thrombosis, arterial occlusions and aneurisms probably plays an important role. Our findings suggest that peripheral deep, but not superficial, thrombophlebitis might be a risk factor for CNS involvement in BD.

Our study population was recruited from several medical centers in Israel, and every patient who fulfilled the International Study Group criteria for BD (8) was included in the study. The patients had heterogeneous ethnic origins, and included Jewish (76.5%) and Arabic (23.5%) subjects. We therefore assume that our study population largely reflects the spectrum of BD in Israel.

Since our study was retrospective, it may not be applicable to the characterisation of patients at disease onset. Still, our results point to certain patterns of disease expression which can be recognized during disease evolution. It might be argued that the differences between factors seen here could have resulted from the dif-

ferent disease durations of the patients. To examine that point we checked for the presence of a linear correlation between the various factors and disease duration, and found no such correlation. We therefore conclude that the factor patterns are not dependent on the duration of the disease.

Two of the factors contained negative correlations. To explore whether those negative correlations were a result of mutually exclusive subgroups, we analyzed the factors separately for sex, age at onset and the presence of HLA-B5. Although the number of patients was too low to allow stringent conclusions to be drawn, the negative correlations did not disappear in any of the subgroups. It remains possible that those negative correlations are to be explained by another variable, which must be sought for.

In conclusion, the application of factor analysis revealed possible associations between distinct types of skin lesions, or venous thrombosis, to other disease manifestations, some of which were sex, age at onset, or HLA-specific, in Behçet's disease. More information on the pattern of BD expression could be obtained by applying this type of statistical method to the evaluation of data on patients from other parts of the world.

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