Acta Dermatovener (Stockholm) 57: 243–245, 1977

# THE HISTOCOMPATIBILITY ANTIGENS IN PATIENTS WITH BEHÇET'S DISEASE

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*Abstract.* Twenty-one patients with Behçet's disease were typed for HLA antigens. The controls were 50 subjects randomly chosen from a local population and 24 apparently healthy subjects of the same ethnic groupings as those of the patients. The study revealed significant differences in the frequencies of various antigens in the above three groups, the most obvious of them related to HLA-B5 and HLA-Bw35. HLA-B5 was demonstrated in 71% of the patients as compared with 18% in the local population group and 12.5% in the ethnically related healthy subjects. The incidences of HLA-Bw35 were 66.7%, 32% and 37.5% respectively. In 86% of the patients, at least one of these two antigens was present. It is suggested that besides contributing to the understanding of the disease process, the determining of associated specific antigens may constitute a further diagnostic acid in doubtful cases of Behçet's disease.

*Key words:* Behçet's disease; Race relations; Histocompatibility antigens

The geographical distribution of Behçet's disease, its racial predilection, as well as the occurrence of the disease in a number of siblings together with male predominance (1, 2, 5, 8), are all suggestive of a genetic susceptibility.

We consider, therefore, that a study of the histocompatibility system in different groups of patients with this malady may shed some light on this question.

## SUBJECTS AND METHODS

Twenty-one patients with Behçet's disease (19 males and 3 women) were typed for HLA antigens. Their ages ranged from 21 to 61 years and the duration of their disease varied from 3 to 34 years. The diagnosis in these cases was based upon the presence of at least two of the cardinal and one of the other symptoms recognized as part of the disease picture. The hyperreactivity of the skin to intracutaneous injection of saline solution (7) and the recurrent nature of the symptoms have also been taken into consideration in establishing the diagnosis.

Nine of the 21 patients presented the complete disease picture and 12 belonged to the incomplete type. All the latter cases lacked the ocular symptoms. In two instances, the patients were brothers.

There were 9 Israel-born Arabs (7 Moslems and 2 Christians); 9 North African Jews (7 from Morocco, 1 from Egypt and 1 from Tunis); 2 Israel-born Jews (1 of Syrian and 1 of Moroccan origin). The remaining patient was a Jew born in Poland.

The control groups consisted of (1) 50 subjects randomly chosen from our local population, (2) 24 apparently healthy subjects related to similar ethnic groups as those of the patients.

Blood samples from patients and controls were collected in heparinized tubes. Lymphocytes were isolated according to the method of Thorsby & Bratilie (15), using a Ficoll–Urografin mixture (Urografin, Schering A. G. Berlin, Germany) instead of Ficoll–Isopaque.

Histocompatibility antigens were determined by the microlymphocytotoxicity test, NIH standard technique (12). The typing reagents were obtained from the National Institute of Health ((NIH) Serum Bank.

The following antigens were determined:

First locus: HLA-A1, A2, A3, A9, A10, A11, A28, Aw29, Aw30.

Second locus: HLA-B5, B7, B8, B12, B13, B14, B18, B27, Bw15, Bw16, Bw17, Bw21, Bw22, Bw35 and Bw40.

The statistical analysis included a parametric test (test for proportions) and non-parametric test ($X^2$ test). Yates' correction was applied in our study.

## RESULTS

The frequencies of HLA antigens in the three tested groups are shown in Table 1.

As compared with the control groups, patients with Behçet's disease reveal a significant increase in the frequencies of HLA-B5 and HLA-Bw35 ($\alpha$ is very small) and a decrease in those of HLA-A1,

Table I. *Frequencies of HLA antigens*

No. of population group: 50; no. of ethnically related group: 24; no. of patients: 21. N.S.=not significant

| Antigens | Subjects | | | | | | Significance | |
|---|---|---|---|---|---|---|---|---|
| | Population | % | Healthy | % | Patients | % | Test for proportion | $\chi^2$ test |
| HLA-A1 | 17 | (34) | 11 | (45) | 5 | (23.8) | 2% | N.S. |
| HLA-A2 | 18 | (36) | 11 | (45) | 11 | (52.4) | 6% | N.S. |
| HLA-A28 | 4 | (8) | 1 | (4.16) | 1 | (4.76) | N.S. | N.S. |
| HLA-A3 | 9 | (18) | 4 | (16.6) | 0 | (0) | 6% | N.S. |
| HLA-A9 | 15 | (30) | 7 | (29) | 6 | (28.6) | N.S. | N.S. |
| HLA-A10 | 10 | (20) | 6 | (25) | 2 | (9.5) | 4% | N.S. |
| HLA-A11 | 7 | (14) | 4 | (16.6) | 2 | (9.5) | N.S. | N.S. |
| HLA-Aw29 | 3 | (6) | 1 | (4.76) | 1 | (4.76) | N.S. | N.S. |
| HLA-Aw30 | 1 | (2) | 0 | (0) | 0 | (0) | N.S. | N.S. |
| HLA-Aw31 | 3 | (6) | 3 | (12.5) | 3 | (14.3) | N.S. | N.S. |
| HLA-B5 | 9 | (18) | 3 | (12.5) | 15 | (71.4) | Sign. for all | Sign. for all |
| HLA-Bw35 | 16 | (32) | 9 | (37.5) | 14 | (66.7) | 2% | Sign. for 10% |
| HLA-B18 | 6 | (12) | 1 | (4.16) | 1 | (4.76) | N.S. | N.S. |
| HLA-Bw15 | 4 | (8) | 0 | (0) | 0 | (0) | N.S. | N.S. |
| HLA-B7 | 7 | (14) | 3 | (12.5) | 0 | (0) | 3% | N.S. |
| HLA-B8 | 9 | (18) | 4 | (16.6) | 1 | (4.76) | 5.8% | 5% |
| HLA-B12 | 7 | (14) | 7 | (29) | 4 | (19) | N.S. | N.S. |
| HLA-B13 | 3 | (6) | 3 | (12.5) | 1 | (4.76) | N.S. | N.S. |
| HLA-B14 | 7 | (14) | 2 | (8.3) | 0 | (0) | N.S. | N.S. |
| HLA-Bw17 | 5 | (10) | 1 | (4.16) | 1 | (4.76) | N.S. | N.S. |
| HLA-B27 | 2 | (4) | 0 | (0) | 0 | (0) | N.S. | N.S. |
| HLA-Bw40 | 4 | (8) | 1 | (4.16) | 1 | (4.76) | N.S. | N.S. |
| HLA-Bw16 | 3 | (6) | 0 | (0) | 1 | (4.76) | N.S. | N.S. |
| HLA-Bw21 | 0 | (0) | 0 | (0) | 1 | (4.76) | N.S. | N.S. |
| HLA-Bw22 | 1 | (2) | 0 | (0) | 1 | (4.76) | N.S. | N.S. |

HLA-A3, HLA-B7 and HLA-B8. HLA-B5 is demonstrated in 71% of the patients as compared with 18% in the local population group and 12.5% in the ethnically related healthy subjects. The incidences of HLA-Bw35 are 66.7%, 32% and 37.5% respectively.

The frequencies of antigens A2, A28, Aw29, Aw30, Aw31, Bw40, B18, Bw17 and B27 differ in the group of patients as compared with those in the local population, whereas in the ethnically related groups they are the same as in the group of patients.

## DISCUSSION

In analysing the results, we tested the hypothesis that each of 25 antigens examined is shared, more or less equally among the investigated groups. The number of patients examined is the minimum required for statistical purposes and may thus lead to slightly biased results.

The study reveals a significant increase in the frequencies of antigens HLA-B5 and HLA-Bw35 in patients with Behçet's disease. This is in agreement with the results of investigations made in a group of Japanese patients (10, 11).

No association of HLA specificities with the severity or type of lesion was noted. It is of interest to mention the differences detected in the frequencies of certain antigens between the patients and the local population group, while the same antigens occurred with equal frequency in the patients and the ethnically related groups. We may speculate that these differences in frequency between the patients and the local population group are due to both the illness and to ethnic causes. When using the ethnically related healthy subjects as a control, the ethnic factor was neutralized and the remaining differences were due (possibly) to the disease alone.

The exact mechanism of the association of the antigens HLA-B5 and HLA-Bw35 is unknown. A large number of genes are present in the HLA region, which have a variety of functions (3). The action of HLA may be indirect, by an epistasis phenomenon, or direct by antigenic cross reaction favouring the penetration of an etiological agent. It is also possible that HLA is merely a genetic marker

linked with a locus-governing immune reaction (13).

Behçet's disease is now known to be a systemic disease affecting a number of organ systems (2, 6). Consequently there exists some degree of overlapping with other systemic disorders. This has resulted in considerable controversy regarding the diagnostic criteria needed to establish a firm diagnosis (4, 9, 14).

We feel justified in believing, therefore, that the finding of associated specific histocompatibility antigens may constitute an aid in the diagnosis of doubtful cases of this polysymptomatic process.

## REFERENCES


1. Araki, Y., Inoue, J., Akita, K., Taked, K. & Kato, T.: Statistical survey of Behçet's disease in Japan. I. The results of inquiries into the family history of the victims and clinical symptoms of the disease. Acta Soc Ophthalmol Jap *77:* 464, 1973.
2. Berlin, C.: Behçet's disease as a multiple symptom complex: report of ten cases, Arch Dermatol *82:* 73, 1960.
3. Bodmer, W. F.: Population studies and the measurement of natural selection, with special reference to the HI-A system. Israel J Med Sci *9:* 1503, 1973.
4. Curth, H. O.: Behçet's syndrome, abortive form (?), Arch Derm Syph *54:* 481, 1946.
5. Fowler, T. J., Humpston, D. J., Mussey, A. M. & Small, M.: Behçet's syndrome with neurological manifestations in two sisters, Br Med J *2:* 473, 1968.
6. Haim, S.: Contribution of ocular symptoms in the diagnosis of Behçet's disease: study of 23 cases. Arch Dermatol *98:* 478, 1968.
7. Katzenellenbogen, I.: Survey of 22 cases of Behçet's disease. *In* The Significance of Specific Skin Hyperreactivity. XIII Congr Intern Dermatol, Munich 1967, pp. 321. Springer-Verlag, Berlin, 1968.
8. Korchin, A. D. & Bornstein, B.: Familial Behçet's disease. Harefuah *84:* 130, 1973.
9. Mason, R. M. & Barnes, C. G.: Behçet's syndrome with arthritis. Ann Rheum Dis *28:* 95, 1969.
10. Ohno, S., Aoki, K., Sugiura, S., Nakayama, E., Itakurra, K. & Aizawa, M.: HL-A5 and Behçet's disease. Lancet *2:* 1383, 1973.
11. Ohno, S., Nakayama, E., Sugiura, S., Itakura, K., Aoki, K. & Aizawa, M.: Specific histocompatibility antigens associated with Behçet's disease. Amer J Ophthalmol *80:* 636, 1975.
12. Ray, J. G., Hare, D. B., Pedersen, P. D. & Kayoe, D. E.: Manual of Tissue Typing Techniques, pp. 20. National Institute of Health Bethesda 1974.
13. Seignalet, J., Clot, J., Guilhou, J. J., Dutze, F., Maynadier, J. & Robinet-Lavy, M.: HL-A antigens and some immunologic parameters in psoriasis. Tissue Antigens *4:* 59, 1974.
14. Strachen, R. W & Wigzell, F. W.: Polyarthritis in Behçet's multiple symptom complex. Ann Rheum Dis *22:* 26, 1963.
15. Thorsby, E. & Bratlie, A.: A Rapid Method for Preparation of Pure Lymphocytes Suspension in Histocompatibility Testing, pp. 655. Munksgaard, Copenhagen, 1970.


*Received April 12, 1976*

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