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BRIEF COMMUNICATIONS

A Study of Familial Occurrence of Behçet's Disease With and Without Ocular Lesions

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Purpose: To examine retrospectively the features of Behçet's disease patients with familial occurrence and make a comparison between familial Behçet's patients with ocular lesions and those without ocular lesions.

Methods: We sent questionnaires about Behçet's disease patients with familial occurrence to 114 hospitals that reported treating such patients in previous nationwide hospital surveys, and to 341 hospitals selected at random in Japan.

Results: We obtained reports on 83 Behçet's patients with familial occurrence. The positive rate of HLA-B51 was 53.1%. The positive rate of HLA-B51 among patients with ocular lesions was 64.0%, that in patients without ocular lesions was 14.3%, and that in patients with genital ulcers was 40.9%. The mean birth year and onset year of the patients with ocular symptoms was significantly lower than that of the patients without ocular symptoms. Although there was no significant difference between these two groups, parent–child involvement was more common among the patients without ocular lesions than in those with ocular lesions.

Conclusions: The findings of this study suggest that the number of familial Behçet's disease patients with ocular lesions and high HLA-B51 positivity has been decreasing recently. To elucidate the etiology of familial occurrence, larger scale epidemiological studies and further molecular studies of Behçet's disease are needed. **Jpn J Ophthalmol 2001;45:313–316**

Key Words: Behçet's disease, familial occurrence, HLA-B51, ocular lesions.

Introduction

Behçet's disease is a systemic inflammatory disorder affecting various organs, and is characterized by recurrent oral ulceration, recurrent genital ulceration, eye lesions, and skin lesions. Eye lesions in patients involve different clinical findings, such as uveoretinitis with hypopyon and retinal vasculitis with branch retinal vein occlusion. Ocular lesions are important because in the Japanese diagnostic criteria of Behçet's disease, revised in 1987, patients with typical ocular symptoms and one other major criterion are diagnosed as having the incomplete type of the disease.[1]

On the other hand, the rates of familial Behçet's disease were 1.78% in 1972, 1.84% in 1979, 2.76% in 1984, and 2.23% in 1992 in Japanese nationwide epidemiological surveys carried out four times in the past, by the Behçet's Disease Research Committee of Japan.[2] According to the international study group for Behçet's disease,[3] the sensitivity of family history is 14% in Iran, 34% in Turkey, 3% in Japan, 18% in Tunisia, 6% in the UK, 18% in the USA, and 13% in France.

Because studying the familial occurrence of Behçet's patients will contribute to determining the causative factors in families, we examined the features of patients with familial occurrence in Japan, and made comparisons between familial patients with ocular lesions and those without ocular lesions.

Materials and Methods

We identified 169 patients with familial Behçet's disease from the results of the previous surveys men-

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tioned above, and sent questionnaires to the 114 hospitals they had attended. In addition, we conducted a nationwide hospital survey of familial Behçet's disease by randomly selecting 341 hospitals that have ophthalmology, dermatology, or internal medicine departments from the 9,333 hospitals in Japan, and sent the same questionnaires to them (10 copies of the questionnaires to each hospital). The questionnaires included items about family members with Behçet's disease, including the year of onset, major and minor symptoms, and HLA antigen.

The data were statistically analyzed using Pearson's correlation coefficient, Pearson's corrected chi-square test, and the *t*-test, using the computer software program Statistical Package for Social Sciences (SPSS, 7.5J).

Results

In reply to our survey of the 169 familial Behçet's patients identified in previous surveys, questionnaires were returned by 52 patients (percentage of return: 30.8%). Of the 341 hospitals in our national survey of familial Behçet's patients, 118 hospitals replied (percentage of return: 34.6%). We obtained a total of 208 returns of questionnaires from these two surveys. We selected 83 (41 men; 42 women) returns from patients with definite familial occurrences of Behçet's disease. The positive rate of HLA-B51 was 53.1% (58.8% men; 46.7% women). The number of patients with complete type of the disease was 37, and their positive rate of HLA-B51 was 53.3%. The number of incomplete type patients was 41 and their positive rate of HLA-B51 was 56.3%. There were 5 patients with suspected Behçet's disease. Relatives of family members with the disease consisted of 4 fathers, 17 mothers, 7 sons, 3 daughters, 18 brothers, 17 sisters, 7 uncles or aunts, 2 nieces or nephews, 2 wives or husbands, and 3 others. Pearson's correlation coefficients of birth year, sex, onset year, onset age, type of disease (complete or incomplete), presence of ocular lesions, presence of genital ulcers, and HLA-B51 positivity are shown in Table 1. The presence of ocular lesions had a high positive correlation with type of disease and HLA-B51 positivity, but had a high negative correlation with birth year, onset year, and presence of genital ulcers. While the positive rate of HLA-B51 among patients with ocular lesions was 64.0% (16/25), that among patients with genital ulcers was 40.9% (9/22). Birth year had a high correlation with onset year, and both had a high correlation with type of disease, but only birth year had a high correlation with sex, as shown in Table 1.

Familial Behçet's patients were divided into two groups: patients with ocular lesions and those without ocular lesions. The characteristics of these groups are shown in Table 2. The mean birth year of the patients with ocular symptoms was 1943.05±10.16, and it was significantly lower than that of the patients without ocular symptoms (1951.83±14.74). The mean onset year of the patients with ocular symptoms (1973.33±10.15) was also lower than that of the patients without ocular symptoms (1981.32±8.78). Therefore, the mean onset age showed no significant differences between these two groups, or between the sexes. The positivity of HLA-B51 among the patients with ocular symptoms was significantly higher than that among the patients without ocular symptoms, and the presence of genital ulcer among the patients with ocular symptoms was significantly lower than that of patients without ocular symptoms. Although there was no significant difference between these two groups, the relationship of familial members with Behçet's

Table 1. Correlation Matrix of Familial Behçet's Disease by Pearson's Coefficient

	Birth Year	Sex	Onset Year	Onset Age	Type of Behçets Disease	Ocular Lesion	Genital Ulcer	HLA-B51
Birth year	–	−.263*	.612†	−.597†	−.271*	−.318†	.046	−.154
Sex		–	−.140	.181	.063	−.052	.170	−.063
Onset year			–	.269*	−.290*	−.359*	.049	−.204
Onset age				–	.046	.027	−.011	−.053
Type of Behçet's disease					–	.607†	.491†	.063
Ocular lesion						–	−.326*	.412*
Genital ulcer							–	−.363*
HLA-B51								–

*$P<.05$.
†$P<.01$.

Table 2. Characteristics of Familial Behçet's Disease Patients with and Without Ocular Lesions

	Patients with Ocular Lesions	Patients Without Ocular Lesions	t/χ^2	*P* values
Birth year	1943.05 ± 10.16	1951.38 ± 14.74	−2.978	.004†
Onset year	1973.33 ± 10.15	1981.32 ± 8.78	−3.399	.001†
<1980/≥1980	38/17	10/15	6.061	.014*
Onset age (years)	30.36 ± 9.53	29.76 ± 11.91	.242	.809
% of men (Men/women)	51.8 (29/27)	46.1 (12/14)	.225	.813
% of HLA-B51 positivity (positive/negative)	64.0 (16/9)	14.3 (1/6)	5.428	.02*
Genital ulcers (with/without)	37/19	25/1	8.713	.002†
Route of occurrence				
Parents-to-children/brothers-to-sisters	19/27	12/9	1.455	.228
Fathers-to-children/mother-to-child	5/14	1/11	1.524	.363

*$P<.05$.
†$P<.01$.

disease among the patients without ocular symptoms had a tendency to be parent-to-child, especially mother-to-child.

Discussion

In the findings of this survey of familial Behçet's disease patients, the mean birth year and onset year of the patients with ocular symptoms was significantly lower than that of the patients without ocular symptoms. The positive rate of HLA-B51 among patients with ocular lesions was 64.0% and that in patients without ocular lesions was 14.3%. These findings suggest that the number of familial Behçet's patients with ocular lesions who have high positivity of HLA-B51 has been decreasing, and those without ocular lesions with genital ulcers who have low positivity of HLA-B51 have been increasing in Japan.

From our previous study,[1] we made a cross-record linkage between the 1991 survey and the 1972 and 1984 surveys to determine the positive rate of HLA-B51, and found that the positive rate of HLA-B51 has been decreasing (1972: 71.4%, 1984: 57.8%, 1991: 54.9%). Furthermore, the number of Japanese female Behçet's patients with ocular symptoms and without genital ulcers was 176 in 1972 and 298 in 1992, while the number of Japanese female Behçet's patients without ocular symptoms and with genital ulcers was 298 in 1972 and 725 in 1992.[1] The number of female patients without ocular symptoms and with genital ulcers increased over the 20-year period. These changes in the clinical manifestations of Behçet's disease show a similar tendency to Western findings of low HLA-B51 positivity and a higher presence of genital ulcers.

As in previous study of familial Behçet's disease,[2] the number of patients with mother–child involvement who are HLA-B51 negative has been increasing. Many of these patients have genital ulcers, but fewer have ocular symptoms. This finding may be related to an increase in female patients with Behçet's disease on the whole, but both female patients and male patients reported having mothers with Behçet's disease. Mori et al[4] also reported a case of a mother and child affected with an incomplete type of the disease without ocular symptoms and with genital symptoms, but both were HLA-B51 negative.

We suggest the recent decrease in typical familial Behçet's patients with HLA-B51, and the increase in the number of female patients with genital ulceration and without ocular lesions. Additionally, a new tendency toward a mild type of the disease similar to the Western type, which is difficult to diagnose, has led to the tendency toward overdiagnosis and the appearance of pseudo Behçet's syndrome, particularly in patients who have family members with Behçet's disease.

The molecular genetic examinations for the disease have recently started to include the association between MIC-A gene polymorphism and the HLA-B51 allele.[5] Although the etiology of familial occurrence of Behçet's disease is still unclear, the onset in all cases is certainly triggered by the same external environmental risk factors, and there are some common genetic features, such as HLA-B51 positivity. Further molecular studies are needed to determine the genetic risk factors other than HLA-B51 in the familial occurrence of Behçet's disease. Moreover, a larger scale epidemiological study of familial patients is also needed to elucidate the etiology of this disease.

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