

Originals

## A Study of Clinical Features and the Worsening Factors Among Patients with Behçet's Disease in Japan

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### SUMMARY

A cross-sectional survey of Behçet's disease in Japan was held to investigate the correlation of clinical features and HLA-B51, pathergy test and the worsening factors among patients. The questionnaires were sent to 200 hospitals selected geographically at random in Japan. The diagnosis was made with Japanese Criteria for the classification and patients who did not satisfy the criteria were excluded from the study. The differences in data were analyzed by Pearson's corrected chi-square test, and multiple logistic regression analyses with SPSS.

A total of 180 patients (80 men and 100 women) were used as subjects. The rate of positive HLA-B51 was 57.4% (66.7% in men, 44.8% in women). HLA-B51 positivity was significantly higher in patients with eye lesions than without, and significantly lower in patients with gastrointestinal lesions than without. The rate of positive pathergy test was 53.0% (67.3% in men, 42.4% in women). The pathergy test positivity was significantly higher in male patients, patients with skin lesions, and with central nerve system symptoms. The number of patients with worsening factors affecting the symptoms, such as seasonal influences, infectious states, psychological fatigue and physical fatigue was 88, with significantly more among patients with skin lesions and those with arthritis, and less among those with eye lesions. As the results of multiple regression analyses show, HLA-B51 negativity was most associated with patients with gastrointestinal lesions and the positivity was most associated with male patients. The pathergy test positivity was most associated with male patients. It was suggested that the rates of positive HLA-B51 and pathergy test were significantly higher among male patients. As the worsening factors might be concerned with the etiology of Behçet's disease, this study only provided some suggestions for further examination.

**Key Words** : Behçet's disease, clinical features, HLA-B51, pathergy test, worsening factors

### INTRODUCTION

Behçet's disease is an inflammatory multisystemic disease of unknown etiology and it was reported to be not a chronic, persistent inflammatory disease, but rather one consisting of recurrent attacks of acute inflammation<sup>1)</sup>. Many patients with the disease occur along the ancient

Silk Road from the eastern Mediterranean and Middle and Far Eastern countries to eastern Asia including China, Korea and Japan, and the genetic association with HLA-B51 was markedly reported in these countries<sup>2,3)</sup>. In Japan, the number of patients with Behçet's disease increased remarkably in the late 1950s. Japanese incidence of the disease is now decreasing but there are many patients suffering from the recurrent inflammatory symptoms. In China and Korea, the studies of the disease have recently increased<sup>4,5)</sup>.

The clinical features of the disease vary in different geographic areas in the world<sup>1,3)</sup>. A previous case-control

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study indicated tonsillitis and teeth damage as environment factors connected with the development of the disease<sup>6)</sup>, but few studies of the effect of factors worsening the clinical symptoms existed throughout the world. Therefore, we conducted a survey of patients with Behçet's disease in Japan and investigated the correlation of clinical features and the worsening factors among the patients.

## METHODS

We sent questionnaires to 200 randomly selected hospitals with clinical ophthalmology, dermatology or internal medicine departments, mainly including national hospitals and hospitals belonging to universities in Japan from Hokkaido in the north to Okinawa in the south for a cross-sectional survey of Behçet's disease patients. The questionnaire included items about clinical symptoms of Behçet's disease, factors that worsen the symptoms, as well as birth year, onset year, and positivities on pathergy test and HLA-B51 (Table 1). Disease onset was defined as the time typical symptoms of Behçet's disease developed. According to international criteria for classification, a positive pathergy test is defined an erythematous papule at the prick site 48 hours after the application of a sterile 20 – 22 gauge needle. If patients had a positive pathergy test during the course of the disease, they were regarded as pathergy test positive.

The diagnosis was made with Japanese Criteria for the classification of Behçet's disease (7) and patients who did not satisfy the criteria were excluded from the study. The differences in data were analyzed with Pearson's correlation coefficient, Pearson's corrected chi-square test, and logistic regression analyses with the computer software program Statistical Package for Social Sciences (SPSS, v 11.0 for Windows).

## RESULTS

In reply to our survey, questionnaires of 203 patients were returned and 180 patients met the Japanese Criteria for the classification of Behçet's disease, 23 being excluded. A total of 180 patients (80 men and 100 women) were divided into 71 complete type and 109 incomplete type. The frequency of patients in the active stage of the disease was 31.1%. The mean birth year was  $1945.4 \pm 13.2$ , the oldest patient was born in 1912 and youngest was in 1983. The mean onset year was  $1978.6 \pm 11.1$ , and mean

onset age was  $33.2 \pm 11.1$  yrs. The number of patients with onset age below 20 yrs was 18 (10.0%); 20 – 29 yrs, 49 (27.2%); 30 – 39 yrs, 61 (33.9%); 40 – 49 yrs, 36 (20.2%); 50 – 59 yrs, 15 (8.3%) and with onset age over 60 there was only one patient (0.56%). The clinical features and HLA-B51, pathergy test and the worsening factors among patients with Behçet's disease in Japan are shown in Table 1. The commonest symptom was oral ulceration (99.4%), and then skin lesions (91.6%). The rate of positive HLA-B51 excluding unknown was 57.4% (66.7% in men and 44.8% in women). The rate of positive HLA-B51 was significantly higher in patients with eye lesions than without the lesions and significantly lower in patients with gastrointestinal lesions than without the lesions. The rate of positive pathergy test excluding unknown was 53.0% (67.3% in men and 42.4% in women). Pathergy test positivity was significantly higher in male patients, patients with skin lesions, and patients with central nerve system symptoms. The number of patients with worsening factors affecting the symptoms was 88, and significantly more among patients with skin lesions and arthritis and less among patients with eye lesions. The mean number of worsening factors in each patient was  $2.13 \pm 1.12$  (range 1 – 5). The number of patients who answered concerning seasonal influence including winter, summer and rainy season was 48 (54.5%); physical fatigue, 47 (53.4%); psychological fatigue, 31 (35.2%), infectious states including tonsillitis, common cold-like symptoms or dental disease, 21 (23.9%); sleeping disorder, 20 (22.7%), and influence of foods, 5 (5.7%). The number and frequency of patients with each factor worsening the symptoms are shown in Table 3. The major target symptoms were oral ulceration and skin lesions. Major factors worsening both oral ulceration and skin lesions were physical fatigue and seasonal change. Genital ulceration was extremely rare as a target symptom.

As a results of the multiple regression analyses by HLA-B51, pathergy test and worsening factors shown in Table 4, HLA-B51 negativity was most associated with patients with gastrointestinal lesions and positivity was most associated with male patients. The patients with eye lesions also had high HLA-B51 positivity but not significant. The pathergy test positivity was mostly associated with male patients. There were no significant differences

**Table 1** The questionnaire for patients with Behcet's Disease (in Japanese)

Physician's name (recorder) _____		Name of hospital _____ Address _____		
Name of patient _____	Record number _____	1 Male 2 Female	Date of birth _____	Age _____
Year of onset _____	_____	Familial occurrence 1 Yes : relationship _____ 2 No		
Clinical features  (Circle one for each symptom)	Major			
	(1) Recurrent oral ulceration		1 Yes	2 No 3Unknown
	(2) Skin lesions			
	a Erythema nodosum		1 Yes	2 No 3Unknown
	b Subcutaneous thrombophlebitis		1 Yes	2 No 3Unknown
	c Folliculitis, acne-like lesions		1 Yes	2 No 3Unknown
	(3) Eye lesions			
	a Iridocyclitis		1 Yes	2 No 3Unknown
	b Chorioretinitis		1 Yes	2 No 3Unknown
	c Definite history of iridocyclitis or chorioretinitis		1 Yes	2 No 3Unknown
(4) Genital ulcers		1 Yes	2 No 3Unknown	
Minor				
(5) Arthritis without deformity		1 Yes	2 No 3Unknown	
(6) Gastrointestinal lesions		1 Yes	2 No 3Unknown	
(7) Epididymitis		1 Yes	2 No 3Unknown	
(8) Vascular lesions		1 Yes	2 No 3Unknown	
(9) Central nervous system symptoms		1 Yes	2 No 3Unknown	
Recent activity	1 Active 2 Nonactive	Recent clinical course 1 Active 2 Remittent 3 Stable 4 Unknown		
Pathergy test	1 Positive 2 Negative 3 Unknown	HLA - B51	1 Positive 2 Negative 3 Unknown	HLA antigen HLA - A _____ HLA - B _____ HLA - DR _____ HLA - DQ _____
Worsening factors *				
1 Seasonal change    a Winter    b Summer    c Rainy season				
2 Infectious state    a Tonsillitis    b Common cold-like symptoms    c Dental problems				
3 Psychological fatigue    4 Sleep disorder    5 Physical fatigue    6 Influence of food (    )				
The symptoms influenced by worsening factors *				
1 All symptoms    2 Oral ulceration    3 Skin lesions    4 Eye lesions				
5 Genital ulceration    6 other symptoms (    )				

\* More than one answer may be chosen.

in each variable due to worsening factors.

## DISCUSSION

The diagnosis of Behçet's disease was conducted with the Japanese Criteria for the classification<sup>7)</sup> in the present study. Among Japanese patients, typical eye lesions play an important role in diagnosis and about 10% of Japanese patients were not compatible with the International crite-

ria for the classification<sup>8)</sup>, but the positivities of HLA - B51 and pathergy test among these patients was as high as those among the compatible patients<sup>9)</sup>. In Japanese criteria subcutaneous thrombophlebitis is included in skin lesions, as opposed to International criteria, which exclude it because of low specificity<sup>9)</sup>.

Oral ulceration is usually an initial symptom throughout the world, and is seen in almost all patients (97 - 100%)

**Table 2** The prevalence of clinical features

		Patients No. (%)	HLA - B51 + / - (%)	Pathergy test + / - (%)	Worsening factors With/without (%)
Sex	Men	80 (44.4 %)	26/13 (66.7)	33/16 (67.3) **	39/41 (48.8)
	Women	100 (55.6 %)	13/16 (44.8)	28/38 (42.4)	49/51 (49.0)
Onset age	< 30	68 (37.8 %)	20/10 (66.7)	22/20 (52.4)	29/38 (43.3)
	≥ 30	115 (63.9 %)	19/19 (50.0)	39/34 (53.4)	59/54 (52.2)
Type <sup>+</sup>	Complete	71 (39.4 %)	20/13 (60.6)	28/21 (57.1)	33/38 (46.5)
	Incomplete	109 (60.6 %)	19/16 (54.3)	33/32 (50.8)	53/54 (49.5)
Oral ulceration		179/1 (99.4 %)	39/29 (57.4)	61/54 (53.0)	88/91 (49.2)
Genital ulceration		129/43 (75.0 %)	25/23 (52.1)	46/38 (54.8)	62/67 (48.1)
Eye lesions		108/71 (60.3 %)	31/16 (66.0) *	33/32 (50.8)	45/62 (42.0) *
Skin lesions		163/15 (91.6 %)	38/24 (61.3)	61/49 (55.5) *	85/78 (52.1) *
Arthritis		86/71 (54.8 %)	21/15 (58.3)	34/32 (51.5)	53/33 (61.6) *
Gastrointestinal		36/121 (22.9 %)	3/8 (27.3) *	11/12 (47.8)	17/19 (47.2)
Epididymitis (men)		7/65 (9.7 %)	4/0 (100)	2/3 (40.0)	4/3 (57.1)
Vascular lesions		17/145 (10.5 %)	3/1 (75.0)	9/5 (64.3)	11/6 (64.7)
CNS <sup>++</sup> symptoms		16/144 (10.0 %)	3/4 (42.9)	10/2 (83.3) *	6/10 (37.5)
Positive HLA - B51		39/29 (57.4 %)	---	21/11 (65.6)	15/24 (38.5)
Positive pathergy		61/54 (53.0 %)	21/10 (67.7)	---	34/27 (55.7)
Worsening factors		88/92 (48.9 %)	15/18 (45.5)	34/37 (47.9)	---

<sup>+</sup> diagnosed by Japanese clinical criteria of Behçet's disease<sup>7)</sup>

<sup>++</sup> CNS : Central nerve system

\*  $p < 0.05$  \*\*  $p < 0.01$

**Table 3** Number and frequency of patients with each factor worsening the symptoms

	Seasonal	Infection	Psychological fatigue	Sleep disorder	Physical fatigue	Foods	total
Systemic symptoms	9 (50.0 %)	4 (22.2 %)	8 (44.4 %)	7 (38.9 %)	11 (61.1 %)	1 (5.5 %)	18 (100 %)
Oral ulceration	27 (47.4 %)	3 (5.26 %)	20 (35.1 %)	15 (26.3 %)	38 (66.7 %)	1 (1.75 %)	57 (100 %)
Genital ulceration	0 (0 %)	1 (50 %)	1 (50 %)	0 (0 %)	0 (0 %)	0 (0 %)	2 (100 %)
Eye lesions	10 (71.4 %)	2 (14.3 %)	4 (28.6 %)	7 (50.0 %)	2 (14.3 %)	5 (35.7 %)	14 (100 %)
Skin lesions	22 (57.9 %)	6 (15.8 %)	16 (42.1 %)	16 (42.1 %)	25 (65.8 %)	8 (21.1 %)	38 (100 %)
Arthritis	5 (71.4 %)	1 (14.3 %)	2 (28.6 %)	2 (28.6 %)	5 (71.4 %)	1 (14.3 %)	7 (100 %)
Gastro - intestinal	2 (66.7 %)	1 (33.3 %)	2 (66.7 %)	0 (0 %)	0 (0 %)	0 (0 %)	3 (100 %)
CNS* symptoms	0 (0 %)	0 (0 %)	1 (50 %)	1 (50 %)	1 (50 %)	1 (50 %)	2 (100 %)

\* CNS symptoms : Central nerve system symptoms

in the clinical course<sup>1,2)</sup>. Typical ocular lesions occurring in the uvea and retina were more common in Japan than in other countries. The result of a nation - wide survey in

Japan showed the proportion of patients with ocular lesions was 69.1%<sup>7)</sup>, a little higher than the 60.3% in the current study. Chang et al. reported that ocular

**Table 4** Multiple logistic regression analysis by HLA-B51, pathergy test and worsening factors

	B	S.E.	Wald	p
<u>HLA-B51</u>				
Sex (male patients)	1.325	0.644	4.235	0.040 **
Eye lesions	1.280	0.687	3.472	0.062 *
Skin lesions	1.728	1.281	1.819	0.177
Gastrointestinal	-2.368	0.930	6.487	0.011 **
Epididymitis	7.753	28.113	0.076	0.783
Constant	-16.811	56.237	0.089	0.765
<u>Pathergy test</u>				
Sex (male patients)	0.994	0.432	5.293	0.021 **
Skin Lesions	16.876	45.441	0.138	0.710
CNS symptoms	8.694	25.689	0.115	0.735
Constant	-35.877	85.698	0.175	0.675
<u>Worsening factors</u>				
Eye lesions	-0.541	0.336	2.595	0.107
Skin lesions	0.860	0.730	1.387	0.239
Arthritis	0.547	0.337	2.642	0.104
Constant	-1.130	0.995	1.291	0.256

\*\*  $p < 0.05$ , \*  $p < 0.1$

B : Regression coefficient, S.E. : Standard error,

Wald : Wald-test value, p : p-value (Significance)

lesions were found in 23.3% in Korea<sup>5)</sup>. In southern Chinese patients, eye disease was diagnosed in 35% of cases<sup>4)</sup>. Frequency of ocular involvement was reported to be 28.9% among Turkish patients<sup>10)</sup>, 48% in German patients<sup>11)</sup>, and 43.8% in northwestern Spain<sup>12)</sup>. The association factors with HLA-B51 in Japanese patients were previously reported to be complete type, male patients, patients with onset age below 30, and without gastrointestinal lesions<sup>7)</sup>. Although there were no significant differences between complete and incomplete types, or onset age below 30 and over 30, there were significant differences between male and female patients, patients with and without gastrointestinal lesions, and patients with and without ocular lesions in the current study. In a previous study of familial Behçet's disease, patients with ocular lesions had significantly higher positivity of HLA-B51 than those without<sup>13)</sup>, but there were no significant differences in most patients in the nationwide epidemiological survey in Japan<sup>7)</sup>. Significantly more patients with the positive pathergy test in the current study were in males than in females, more had skin lesions than without, and had central nerve system symptoms. Krause et al. reported that the pathergy-positive and negative patients showed a similar male-female ratio, and no sig-

nificance difference was found between the two groups after examining the clinical characteristics of the patients in Israel<sup>14)</sup>. According to a Korean study by Chang et al., there was no significant difference between the positive pathergy reaction and the clinical variables but a tendency for more male patients than female<sup>15)</sup>.

There are a few previous studies about worsening factors. From the case control studies by Nakae et al., ten factors were significant in higher frequencies in the patients group<sup>6)</sup>. All factors suggested that the patients were in somewhat infectious or immunologic states. There were some previous reports concerning an association between Behçet's disease and infectious disease. Endoh et al. reported the case of an 80-year old patient who presented with a fever of unknown origin, and had recurrent and intractable infectious disease with neutrophil dominant leukocytosis<sup>16)</sup>. This patient displayed four typical major symptoms and was diagnosed with Behçet's disease 3 years after their first appearance<sup>16)</sup>. Kiraz et al. reported that six patients with Behçet's disease had anti-B19 IgM antibodies in their serum samples indicating a recent infection, and suggested that viral infections had been postulated as factors triggering the disease<sup>17)</sup>. Akaogi et al. reported that serum hepatitis B virus-DNA and GB virus-C-RNA was detected more frequently in patients than in blood donors<sup>18)</sup>. Mizushima et al. reported that severe symptoms of Behçet's disease were induced after dental treatment in 2 patients and were probably induced by the streptococcal antigen skin test in 4 patients, and suggested a possible role of the streptococcus in the pathogenesis of Behçet's disease<sup>19)</sup>. In the present study, psychological and physical fatigue were dominant factors, as well as infectious disease. Recurrent aphthous stomatitis, the most common lesion among patients, is caused by different factors including trauma, stress, family history, food hypersensitivity, infectious or immunologic factors and so on<sup>20)</sup>. Heat shock protein developed by stresses, has been implicated in the etiology of Behçet's disease, and an increase in HSP expression was found at lesional skin sites in Behçet's disease<sup>21)</sup>, so that the occurrence of symptoms of the disease are related to multiple complex factors, such as genetic, environmental, immunologic, and allergic states.

We investigated the association of clinical features and HLA-B51, pathergy test and worsening factors in patients with Behçet's disease in Japan but the disease

activities in Japanese patients have recently declined and it is difficult to examine the real time active changing state of onset of the disease. As the worsening factors might be concerned with the etiology of Behçet's disease, the current study only gave some suggestions for further examination.

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