[Environmental Health and Preventive Medicine 4, 130-134, October, 1999]

*Original Article*

# A Study of Comparison between the Nationwide Epidemiological Survey in 1991 and Previous Surveys on Behçet's Disease in Japan

Midori NISHIYAMA*1, Kimihiro NAKAE*1, Satoru YUKAWA*1,
Takashi HASHIMOTO*2, Goro INABA*2, Manabu MOCHIZUKI*3 and Tsuyoshi SAKANE*4

*1 *Department of Public Health, Dokky University School of Medicine, Tochigi*
*2 *Department of Internal Medicine, Teikyo University School of Medicine, Tokyo*
*3 *Department of Ophthalmology, Tokyo Medical and Dental University, Tokyo*
*4 *Institute of Medical Science, St. Marianna University School of Medicine, Kanagawa*

## Abstract

The 4th nationwide epidemiological survey on Behçet disease (BD), which included all patients with BD at 1,200 hospitals selected at random from 10,081 hospitals in Japan, was carried out by the BD Research Committee of the Ministry of Health and Welfare in 1991 to examine the epidemiological features of BD in Japan by comparing with previous surveys.

3,938 patients from these hospitals were examined by the Japanese diagnostic criteria of BD (JCBD) revised in 1987 and the International criteria for classification of BD (ICBD). Among these 3,938 patients, 622 patients were only suspected of having BD or clinical signs of the disease were unknown, and most of these patients were incompatible with the ICBD. So these patients were excluded from the study of epidemiological features.

The average patients age has risen 7-8 years over the last 20 years and the average age of onset in both sexes increased by about 3 years from 1972 to 1991. While a decrease in the sex ratio was seen in the complete-type and the incomplete-type BD without ocular symptoms, a sustained high sex ratio was shown in incomplete-type BD with ocular symptoms. The positive rate of HLA-B51 antigen was 54.9% (men: 56.9%, women: 52.2%) significantly higher than the 15-16% in healthy subjects but it might have been gradually decreasing. Also the clinical course of BD has become too mild for prognosis. According to these epidemiological features of BD, the clinical manifestation of BD in Japan might have become the Western type of BD.

**Key words:** Behçet's disease, epidemiological features, sex ratio, HLA-B51, ocular symptoms

## Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder affecting various organs. Most patients with Behçet's disease are of Oriental or Mediterranean origin. Japan has one of the highest incidences of BD world-wide (1)(2). Nationwide epidemiological surveys have been carried out by the BD Research Committee of Japan (Ministry of Health and Welfare) three times in the past; in 1972, 1979 and 1984 (3)(4)(5)(6)(7). The clinical manifestation of BD has changed during these twenty years in Japan. The recent epidemiological findings in Japan are presented in this paper following the 4th nationwide epidemiological survey in 1991(8).

Received Mar. 19 1999/Accepted Jul. 16 1999
Reprint requests to: Midori NISHIYAMA,
Department of Public Health, Dokkyo Univ. School of Medicine, Mibu, Tochigi, 321-0293, Japan.
TEL: +81(282)87-2133 FAX: +81(282)86-2873
e-mail: m-nishi@dokkyomed.ac.jp

## Methods

A working group for the 1991 surveys was established in the BD Research Committee of the Ministry of Health and Welfare to examine the epidemiological features of BD. The clinical diagnostic guidelines, a medical questionnaire and other methodology essential to the survey, were examined by the group. The nationwide hospital survey included all patients with BD treated in 1991 at 1,200 hospitals selected at random from 10,081 hospitals in Japan. The clinical diagnostic guidelines and medical questionnaires were sent to these hospitals, and doctors were requested to provide individual medical data of the patients with BD in the questionnaire. From the responses of these hospitals, 3,938 patients (men: 1,879, women: 2,059) were examined by the Japanese diagnostic criteria of BD (JCBD) revised in 1987 (9)(10) as shown in Table 1. Furthermore, the compatibility of the Japanese to the International criteria for classification of BD (ICBD)(10) as shown in Table 2 was examined.

This study attempted to examine the epidemiological features such as sex and age trends, the positive rate of HLA-B51 and the tendency toward mild Behçet's disease from the 1991 survey by making comparison from the findings of the past three surveys. In this survey subjects who were diagnosed as having only suspected BD and patients whose clinical signs of the disease were unknown were excluded from the study of epidemiological features.

We, especially, made a cross-record linkage between the 1991 survey and the 1972 and 1984 surveys to determine the positive rate of HLA-B51 in the past. And a comparison of the sex ratio between the survey of 1972 and that of 1991 was analyzed statistically with the chi-square test using the computer software HALBAU (N88-Japanese BASIC).

**Table 1 Japanese clinical criteria of the Behçet disease by the research committee of Japan revised in 1987**

| | |
|---|---|
| Major | Recurrent aphthous ulceration of the oral mucous membrane |
| | Skin lesions |
| | Erythema nodosum |
| | Subcutaneous thrombophlebitis |
| | Folliculitis, acne-like lesions |
| | Cutaneous hypersensitivity |
| | Eye lesions |
| | Iridocyclitis |
| | Chorioretinitis, retino-uveitis |
| | Definite history of chorioretinitis or retino-uveitis |
| | Genital ulcers |
| Minor | Arthritis without deformity and ankylosis |
| | Gastrointestinal lesions characterized by ileocaecal ulcers |
| | Epididymitis |
| | Vascular lesions |
| | Central nervous system symptoms |
| Diagnosis | |
| Complete | Four major features |
| Incomplete | Three major features or two major + two minor<br>or typical ocular symptom + one major or two minor features |

**Table 2 International criteria for classification of Behçet's disease (by international study group of Behçet's disease,1991)**

| | |
|---|---|
| Recurrent oral ulceration | Minor aphthous |
| | Major aphthous or herpetiform ulceration observed by a physician or reported reliably by patient<br>Recurrent at least three times in one 12-month period |
| Plus two of | |
| Recurrent genital ulceration | Recurrent genital aphthous ulceration or scarring, especially in males, observed by physician or reliably reported by patient |
| Eye lesions | a. Aterior uveitis<br>b. Posterior uveitis<br>c. Cells in vitreous on slit lamp examination<br>or<br>d. Retinal vasculitis observed by qualified physician(ophthalmologist) |
| Skin lesions | a. Erythema-nodosum-like lesions observed by physician or reliably reported by patient<br>b. Pseuofolliculitis<br>c. Papulopustular lesions<br>or<br>d. Acneiform nodules consistent with Behçet's disease observed by a physician and in post-adolescent patients not receiving corticosteroids |
| Positive pathergy test | An erythematous papule, >2mm, at the prick site 48hr after the application of a sterile needle, 20-22 gauge, which obliquely penetrated avascular skin to depth of 5mm: read by physician at 48 hr |

## Results

A nationwide epidemiological survey on Behçet's disease (BD) in Japan were carried out in 1991, and 3,938 (men: 1,879, women: 2,059) patients were obtained from this hospital survey. According to the Japanese diagnostic criteria of BD revised in 1987 by the BD Research Committee of Japan (JCBD, Table 1.), the 3,938 patients included 1,139 (28.9%) with complete type and 2,177 (55.3%) with incomplete type (1,152 with ocular symptoms and 1,025 without ocular symptoms), 332 (8.4%) with suspected or possible type and 290 (4%) unknown type.

The compatibility of the Japanese to ICBD (Table 2.) and that of the positive rates of HLA-B51 are shown by types of patients among the 3,938 cases in Table 3. Among these 3,938 patients, 923 (23.4%) were not compatible with the ICBD. Among the 3,316 patients with complete-type or incomplete-type, 356 patients (10.7%) did not match with the ICBD. Among the 356 patients who did not match with the ICBD, 300 had the incomplete-type with ocular symptoms. On the other hand, the positive rate of HLA-B51 was more than 50% in all types compatible with the ICBD and the incomplete-type with ocular symptoms which is incompatible with the ICBD.

Among 622 patients who were diagnosed as having suspected BD and the patients whose clinical signs of the disease were unknown, 567 patients were incompatible with the ICBD. So these patients were excluded from the study of epidemiological features. The number of subjects of this study was 3,316 patients (men: 1,638, women: 1,678).

The average age of the 3,316 patients was 46.5 (11.7SD) years and that of 1,638 male patients was 44.5 (11.2SD) years and 1,678 female patients was 48.4 (11.9SD) years. Positive rate of HLA-B51 antigen was 54.9% (men: 56.9%, women: 52.2% ) significantly higher than the 15-16% among healthy Japanese.

1. Sex and age trends

The sex ratio (male: female) of patients with BD in 1991 was 0.98 (1.07 for the complete-type and 0.93 for the incomplete-type BD) as shown in Table 4. A remarkable difference was found between the rate of incomplete-type with ocular symptoms (1.87) and incomplete-type without ocular symptoms (0.41), and

**Table 3 Compatibility of Japanese with international criteria (ICBD) and positive rate of HLA-B51**

| Japanese type of BD | Compatibility with ICBD | | | |
|---|---|---|---|---|
| | compatible | positive rate of HLA-B51 | incompatible | positive rate of HLA-B51 |
| complete | 1,139(28.9%) | 58.3% | 0( 0.0%) | — |
| incomplete | | | | |
| with ocular symptoms | 852(21.6%) | 51.1% | 300( 7.6%) | 52.3% |
| without ocular symptoms | 969(24.6%) | 52.4% | 56( 1.4%) | 33.3% |
| suspected or possible | 41( 1.0%) | 57.1% | 291( 7.4%) | 29.0% |
| unknown type | 14( 0.4%) | 50.0% | 276( 7.0%) | 50.0% |
| total | 3,015(76.6%) | 54.5% | 923(23.4%) | 45.9% |

Table 4 Transition of the sex ratio and disease type

| Disease type | male/female(numbers) | | | sex ratio | | | $\chi^2$ (95% confidence intervals) |
|---|---|---|---|---|---|---|---|
| | 1972 | 1984 | 1991 | 1972 | 1984 | 1991 | 1972 vs. 1991 |
| total | 1169/862 | 1278/1357 | 1638/1678 | 1.36 | 0.94 | 0.98 | 33.6 (1.24, 1.56)** |
| complete-type | 594/334 | 564/495 | 588/551 | 1.78 | 1.14 | 1.07 | 32.0(1.39, 2.00)** |
| incomplete-type | 574/528 | 714/862 | 1050/1127 | 1.09 | 0.83 | 0.93 | 4.35(1.01, 1.35) |
| incomplete-type | | | | | | | |
| with ocular symptoms(ocu.) | 403/230 | 474/302 | 750/402 | 1.75 | 1.57 | 1.87 | 0.37(0.76, 1.16) |
| without ocu. | 172/298 | 240/560 | 300/725 | 0.58 | 0.43 | 0.41 | 8.01(1.10, 1.77)* |
| with genital ulcers (gen.) | 260/352 | 289/616 | 338/806 | 0.74 | 0.47 | 0.42 | 29.7(1.43, 2.17)** |
| without gen. | 315/176 | 325/176 | 712/321 | 1.79 | 1.85 | 2.22 | 3.45(0.64, 1.02) |
| with both ocu. and gen. | 88/54 | 71/85 | 73/104 | 1.63 | 0.84 | 0.70 | 13.5(1.44, 3.75)** |
| with ocu. and without gen. | 315/176 | 311/151 | 674/298 | 1.79 | 2.06 | 2.26 | 4.01(0.63, 1.00) |
| without ocu. and with gen. | 172/298 | 218/531 | 300/725 | 0.58 | 0.41 | 0.41 | 8.01(1.10, 1.77)* |

*p value<0.01, **p value<0.001

Table 5 Positive rate of HLA-B51 by sex and age of onset

| Age of onset | positive rate of HLA-B51% (numbers) | | |
|---|---|---|---|
| | Male | Female | Both sexes |
| 0 ~ 29 | 65.5% (72/110) | 54.1% (33/61) | 61.4% (105/171) |
| 30+ | 52.7% (117/222) | 51.6% (97/188) | 52.2% (214/410) |
| All ages | 56.9% (189/332) | 52.2% (130/249) | 54.9% (319/581) |

Table 6 Major and minor symptoms and HLA-B51

| Major or minor symptoms | Proportion of the patients | | |
|---|---|---|---|
| | with the symptoms (%) | | positive rate of HLA-B51(%) |
| | 1972 | 1991 | |
| Major symptoms | | | |
| Aphthous ulceration | 96.0 | 98.2 | 53.3 |
| Skin lesion | 82.7 | 87.1 | 56.2 |
| Ocular symptoms | 67.4 | 69.1 | 54.5 |
| Genital ulcers | 72.3 | 73.2 | 54.7 |
| Minor symptoms | | | |
| Arthritis | 54.1 | 56.9 | 54.4 |
| Epididymitis | 6.2 | 6.0 | 67.6 |
| Gastrointestinal lesion | 24.6 | 15.5 | 43.5 |
| Vascular lesion | 7.4 | 8.9 | 51.4 |
| CNS* symptoms | 12.7 | 11.0 | 56.7 |
| Positive pathergy test | 75.1. | 43.8 | 55.1 |

*CNS: central nervous system

Patients in whom the manifestation of symptoms was unknown were excluded.

Table 7 Transition of the positive rate of HLA-B51

| | positive rate of HLA-B51 % (numbers) | | |
|---|---|---|---|
| | total | male | female |
| 1972 | 71.4% (10/14) | 70.0% | 75.5% |
| 1984 | 58.1% (52/90) | 58.1% | 57.4% |
| 1991 | 54.9% (319/581) | 56.9% | 52.2% |

Table 8 Clinical course during the past one year

| Clinical course | Proportion of the patients (%) | | positive rate of HLA-B51 (%) |
|---|---|---|---|
| | 1972 | 1991 | |
| No attack or amelioration | 24.5 | 57.0 | 61.5 |
| unchanged | 42.0 | 31.7 | 48.7 |
| Deterioration | 30.1 | 9.1 | 46.9 |
| Death | 1.0 | 0.4 | 33.3 |
| Other | 2.4 | 1.8 | 41.2 |

also between the rate of incomplete-type with genital ulcers (0.42) and incomplete-type without genital ulcers (2.22).

A decrease in the sex ratio was seen in the complete-type (1.78 in 1972, 1.14 in 1984, and 1.07 in1991) and also in the incomplete-type without ocular symptoms (0.58 in 1972, 0.43 in 1984, and 0.41 in 1991), incomplete-type BD with genital ulcers (0.74 in 1972, 0.42 in 1984, and 0.42 in 1991) and incomplete-type BD with both ocular symptoms and genital ulcers (1.63 in 1972, 0.84 in 1984, and 0.70 in 1991). A considerably high and sustained trend was shown in incomplete-type BD with ocular symptoms (1.75 in 1972, 1.57 in 1984, and 1.87 in 1991), incomplete-type without genital ulcers (1.79 in 1972, 1.85 in 1984 and 2.22 in 1991) and incomplete-type with ocular symptoms without genital ulcers (1.79 in 1972, 2.06 in 1984 and 2.26 in 1991), as shown in Table 4. The maintenance of a high sex ratio in the incomplete type with ocular symptoms seemed to be due to a high and increased proportion of male patients without genital ulcers and with ocular symptoms (57.9% in 1972, 64.2% in 1991).

The average age has risen 7-8 years over the last 20 years (an increase of 7.2 years in men and 8.1 years in women). The average age of onset was 35.7 years (34.6 years in men and 36.8 years in women). The average age of onset in both sexes increased by about 3 years from 1972 to 1991 (3.3 years up in men and 2.7 years up in women). Eighty-five percent of the 3,316 patients had developed the disease between the ages of 20 and 49 years. The proportion of patients who developed the disease under the age of 10 years was very low at only 0.44%.

2. The positive rate of HLA-B51

Table 5 shows the positive rate of HLA-B51 in patients with BD by sex and onset age. The positive rate of HLA-B51 was 54.9% in both sexes (56.9% in men and 52.2% in women). The positive rate of HLA-B51 was lower in women. The proportion of HLA-B51 in patients who developed the disease under 30 years of age was higher than those whose onset was at an age above 30 years (61.4% vs. 52.2%). The incidence of 65.5% in men whose age of onset was under 30 was remarkably higher than the 51-54% seen in the other sex-age groups. No difference in the positive rate in the healthy controls was found between both sexes or among any of the age groups, i.e., about 15-16% in Japan.

Table 6 shows the proportion of the patients with the symptoms as well as the positive rate of HLA-B51 of patients who had each symptom. The symptom with the highest positive rate of HLA-B51 was epididymitis (67.6%). A range of 51-57% was found in major or minor symptoms except for gastrointestinal lesions (43.5%). BD with central nervous system symptoms has been known to show a high positive rate of HLA-

B51, but in this survey, it was 56.7%. The positive rate of HLA-B51 in the incomplete-type with or without genital ulcers was 48.5% or 52.6%.

We made a cross-record linkage between the 1991 survey and the 1972 and 1984 surveys to determine the positive rate of HLA-B51 in the past. The results are shown in Table 7. The positive rate in 1972 is estimated at 71.4% and that in 1984 at 58.1%. The positive rate of HLA-B51 has decreased recently.

3. Tendency toward mild Behçet's disease

The clinical course of 3,316 patients during 1991 compared with the course of those in 1972 is shown in Table 8. An increase of "no attack or amelioration" and a decrease of "unchanged" or "deterioration" was found in 1991 in comparison with the results of 1972. The mortality rate was reduced from 1.0% in 1972 to 0.4% in 1991. The positive rate of HLA-B51 was significantly higher at 60-62% in "no attack or amelioration" than the 47-49% in "unchanged" or "deterioration".

## Discussion

We examined the recent epidemiological features of Behçet's disease in Japan. An increase in the number of female patients, a decrease in the positive rate of HLA-B51 and a tendency toward mild BD were worthy of attention. The sex ratio (Male/Female) of both the complete and incomplete types decreased for about twenty years, but the sex ratio of the incomplete type with ocular symptoms and without genital ulcers increased. So it means that the female patients without ocular symptoms and with genital ulcers increased. We also examined the recent epidemiological features of familial Behçet's disease in Japan before (11). As a result, the number of patients with mother-child involvement with low HLA-B51 positivity, was recently found to be increasing. Many of these patients had genital ulcers, but fewer had ocular symptoms. This result may be related to an increase in female patients with Behçet's disease on the whole.

It was demonstrated that BD patients positive for HLA-B51 were more likely to develop BD (12). A highly significant association between HLA-B51 and BD was found in the coastal countries of the Mediterranean Sea and Middle Eastern countries as well as in Japan (13)(14)(15). Moreover, the HLA antigen has recently been identified as comprising three alleles, HLA-B*5101, HLA-B*5102 and HLA-B*5103, and it has been reported that 46 Japanese HLA-B51-positive patients with BD were found to carry HLA-B*5101 (16). HLA is inherited from either parent and it is worthy of attention as a genetic factor. According to Takeno et al., neutrophils of HLA-B51 transgenic mice have high activity (17). Therefore, the groups of patients with a high positive rate of B51 (i.e., male patients with an onset age below 30 years or with epididymitis) might provide a clue to the etiology of BD. The groups with a low positive rate of B51 (i.e.,with gastrointestinal lesions) might have low sensitivity to BD and be heavily exposed to an etiological agent, or might include more non-BD patients.

Despite these interesting associations, North American patients were said to share no increased link to HLA-B51 by O'Duffy (18). There are a lot of another differences of clinical manifestation between the Eastern type and the Western type of BD. In the Western countries such as the UK, France and the USA, the sensitivity of genital ulcers is higher and that of ocular lesions is lower than in the Eastern countries such like Japan and Iran (10). So the diagnostic criteria were quite different in each countries. The International study group of BD examined the five sets of diagnostic criteria: (1) diagnostic criteria by Mason and Barnes who permit diagnosis in the absence of oral ulceration (19), (2) the JCBD that emphasizes ocular involvement (Table 1.)(9), (3) O'Duffy who requires oral or genital ulceration for diagnosis and emphasizes the presence of vasculitis (20), (4) Zhang who retains only the original three features as major criteria (21), and (5) Dilsen and his colleagues who emphasize the importance of the pathergy test (22) and established the Internationally agreed criteria, that is the International criteria for classification of BD (ICBD)(Table 2.)(10).

In this study, the incomplete type BD with ocular symptoms (the sex ratio of which was high) had a high positive rate of HLA-B51 similar to the complete type BD, but many cases were incompatible with the ICBD. While the positive rate of HLA-B51 in both incomplete-type without ocular symptoms and the suspected cases was low (29-33%). One of the differences between the JCBD and ICBD is the level of importance attached to the ocular symptoms. Many male patients have ocular symptoms rather than genital ulcers, as mentioned above. The significance of the ocular symptoms in diagnosis should be examined in the future.

Many studies have been conducted to determine the etiology of BD (23)(24), but the underlying cause is still unknown. We consider that HLA-B51 is associated in some way with the etiology. We suggest that the number of typical BD patients with HLA-B51 has been decreasing and the number of female patients with genital ulceration and without ocular lesion has been increasing recently. Added to this decrease in the typical patients, there is a tendency towards mild BD, which is difficult to diagnose, thereby leading to the problem of over-diagnosis and the appearance of pseudo-Behçet's syndrome (25). According to these epidemiological features of BD, the clinical manifestation of BD in Japan might have become the Western type of BD based on patients with the low positivity in HLA-B51, the high sensitivity of genital ulcers and the low sensitivity of ocular lesions.

## Acknowlegements

This work was supported by the Ministry of Health and Welfare, Grant-in Aid for the BD Research Committee, Japan, and in part by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research (C), Japan, No.11670388. We wish to express our sincere thanks to all members of the BD Research Commitee of Japan.

## References

1) Editorial Board. Behçet's Disease. The Lancet, 1989: 1 (8641): 761-2
2) Ohno. S. Behçet's disease in the world, ed.Inaba.G, Tokyo; University of Tokyo Press, 1981: 181-6
3) Masuda K, Inaba G, Mizushima H. A Nationwide Survey of Behçet's Disease in Japan: Clinical Survey. Jap J Ophthalmol, 1975; 19: 278-85
4) Maeda K, Nakae K. Recent Epidemiological Review on

Behçet's Disease. Asian Med J 1977; 20: 568-82
5) Nakae K, Maeda K, Agata T. Late trend of Behçet disease in Japan, 1979 reports of Japanese Behçet's disease Research committee, Ministry of Health and Welfare, Japan. 1980: 89-93 (in Japanese)
6) Nakae K, Agata T, Maeda K. Late trend of epidemiological features on Behçet disease, 1984 reports of Japanese Behçet's disease Research committee, Ministry of Health and Welfare, Japan. 1985: 65-9 (in Japanese)
7) Nakae K, Masaki F, Hashimoto T. An epidemiological study on risk factors of Behçet's disease in Japan. Recent progress of epidemiologic study of intractable disease in Japan, ed. by Yanagawa H et al.,The Epidemiology of Intractable Disease Research Committee of Japan, 1992: 175-80
8) Nakae K, Furusawa F, Hashimoto T, Inaba G, Mochizuki M, Sakane T. The 4th nationwide epidemiological surveys on Behçet's disease in Japan:The rate of prevalence and incidence, 1992 reports of Japanese Behçet's disease Research committee, Ministry of Health and Welfare, Japan. 1993: 63-9 (in Japanese)
9) Sakane T, Yamashita N. Diagnosis for Behçet's disease, Japan. J. Clinical and Experimental Med, 1993; 164 (1): 3-7 (in Japanese)
10) International Study Group for Behçet's Disease. Evaluation of diagnostic ("classification") criteria in Behçet's disease: Toward internationally agreed criteria, Behçet's disease: basic and clinical aspect/edited by J. Desmond O'Duffy and Emre Kokmen. New York: M. Dekker, 1991: 11-39
11) Nishiyama N, Nakae K, Hashimoto T, Inaba G, Sakane T. Recent epidemiological features of familial Behçet's disease in Japan. Asian Med J 1996; 39(9): 495-501
12) Plotkin G.R, Calabro J.J, O'Duffy J.D. Behçet's disease,a contemporary synopsis, New York: Futura, 1998
13) Mizuki N, Ohno S, Tanaka H, et al. Association of HLA-B51 and lack of association of class II alleles with Behçet's disease.Tissue Antigens 1992; 40 : 22-30
14) Brautbar C, Chajek T, Ben-Tuvia S, Lamm L, Cohen T. A genetic study of Behçet's disease in Israel. Tissue Antigens 1978; 11: 113-20
15) Balboni A, Pivetti-Peezzi P, Orlando P, et al. Serological and molecular HLA typing in Italian Behçet's patients: Significant association of B51-DR5-DQw3 haplotype. Tissue Antigens 1992; 39: 141-3
16) Mizuki N, Inoko H, Ando H, et al. Behçet's disease associated with one of the HLA-B51 subantigens, HLA-B*5101. Am J Ophthalmol. 1993; 116: 406-9
17) Takeno M, Kariyone A, Yamashita N, et al. Excessive function of peripheral blood neutrophils from patients with Behçet's disease and HLA-B51 transgenic mice, Arthritis and Rheumatism 1995; 38(3): 426-33
18) O'Duffy JD. Behçet's disease: Current opinion in Rheumatology 1994; 6: 39-43
19) Mason RM, Barnes CG. Behçet's syndrome with arthritis. Ann Rheum Dis 1969; 28: 95-103
20) O'Duffy JD. Criteria proposes pour le diagnostic de la maladie de Behçet et notes therapeutiques. Rev Med 1974; 36: 2371-9
21) Zhang X-Q. Our diagnostic criteria for Behçet's disease. Chin J Intern Med 1980; 19: 15 (in Chinese)
22) Dilsen N, Konice M, Aral O. Our diagnostic criteria for Behçet's disease — an overview. In. Lehner T, Barnes CG, eds. Recent Advances in Behçet's Disease. Royal Society of Medicine Services. Int Congr Sympos Series 1986; 103: 177-80
23) Mizushima Y. Recent research into Behçet's disease in Japan, Int. J. Tiss. Reac. 1988; 10(2): 59-65
24) Hasen A, Fortune F, Wilson A, et al. Role of $\gamma\delta$ T cells in pathogenesis and diagnosis of Behçet's disease, Lancet 1996; 347: 789-94
25) Inaba G. Pseudo-Behçet's syndrome, a problem for accurate diagnosis, Japan J Clinical and Experimental Med 1993; 164(1): 26-9 (in Japanese)