Epidemiological Features and Visual Prognosis of Behçet's Disease

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Purpose: Retrospective evaluation of epidemiological features and visual prognosis of patients with Behçet's disease (BD) who visited the University of Tokyo Hospital between 1974 and 1993.

Observations: During the survey period, more than 100 new patients with BD visited the uveitis clinic in each 5-year period. The number of new patients decreased in the most recent 5-year period from 1989 to 1993. Although BD has always been more prevalent in men, the percentage of women has increased to 24.7% (19/77) in the most recent 5-year survey period. The percentage of patients who initially manifested ocular symptoms in their third or fourth decade was more than 70%. The proportion of the incomplete type of BD gradually had increased to 62.3% (48/77) by 1993. Among the extraocular major symptoms, oral aphtha and skin lesions have been frequent and genital ulcer has become less frequent in the last 20 years. The patients whose visual acuity was better than 0.4 at the first visit in the 1984–1993 period had a significantly better visual prognosis than the patients in the previous 10-year period. The main drug therapy consisted of colchicine and cyclophosphamide in the earlier 10-year period, and of colchicine and ciclosporin in the later 10-year period.

Conclusions: Behçet's disease is still one of the most frequently encountered types of endogenous uveitis. There have been some changes in the epidemiological features of the patients with BD over the past 20 years. The introduction of ciclosporin in 1985 is probably responsible for the improvement of the visual prognosis in BD patients. **Jpn J Ophthalmol 1999;43:312–317** © 1999 Japanese Ophthalmological Society

Key Words: Behçet's disease, ciclosporin treatment, epidemiology, visual prognosis.

Introduction

In outpatient clinics of the major Japanese university hospitals, Behçet's disease (BD) is still one of the most frequently encountered types of endogenous uveitis, along with Vogt–Koyanagi–Harada disease and sarcoidosis.[1–6] In the uveitis clinic of the University of Tokyo Hospital, BD was diagnosed in 49 of 394 (12.4%) patients with endogenous uveitis during the 3-year period from 1989 to 1991.[2] In spite of the extreme care taken to control ocular inflammation in these patients, it was difficult to eliminate it completely. In refractory cases, the visual outcome is usually very poor.

Because our clinic has been treating a great number of BD patients for more than 20 years, a long-term evaluation of this disease was thought to be necessary. In the present study, clinical data obtained from BD patients who visited our clinic were retrospectively analyzed regarding epidemiological features and visual prognosis.

Materials and Methods

A total of 399 BD patients with ocular symptoms, who visited the uveitis clinic of the University of Tokyo Hospital between 1974 and 1993, were included in this study. Diagnosis of BD was determined according to the criteria established by the Behçet's

Table 1. Visual Acuity and Frequency in Patients at First Visit

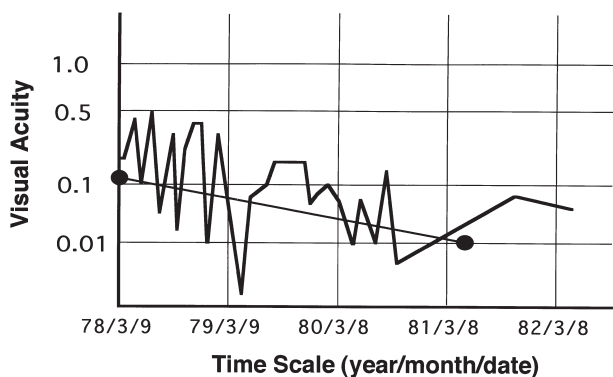| Year of First Visit	Visual Acuity at First Visit	
	0.1–0.4	Better Than 0.4
1974–1983	27 (32)	37 (49)
1984–1993	28 (35)	30 (39)

No. of eyes are in parentheses.

Disease Research Committee of Japan.[7] Three hundred and eighteen patients were men and 81 were women. The patients were divided into four groups by 5-year periods based on the year of the first visit.

Long-term changes in epidemiological features, such as number of patients, sex distribution, age at onset, proportion of complete and incomplete types of the disease, and frequency of the extraocular major symptoms, were tabulated and statistically analyzed by Student's t-test with Welch's correction or the χ^2 test.

In addition, we examined the visual outcome of 122 patients (155 eyes) followed for more than 3 years, whose visual acuity at the first visit was 0.1 or better. We excluded eyes that rapidly recovered their visual acuity after cataract surgery. In 14 patients with unilateral involvement, the fellow normal eye was excluded.

Patients were divided into four groups according to their corrected visual acuity[8,9] and the year of the first visit (Table 1). The following equation was used to determine the time course of changes in visual acuity in a linear form (Figure 1).[10]

$$-\log\log(V_{max}/V) = -\log\log(V_{max}/V_0) + \alpha t$$

where α = rate constant, t = number of days after first visit, V = corrected visual acuity, V_0 = corrected visual acuity at the first visit, and V_{max} = maximum visual acuity. The correlation coefficient between the initial visual acuity and the rate constant α was at a minimum with a V_{max} value of 4.0, and this value was used for the analysis.

The rate constant, α, represents the rate of change of the visual acuity over the period of observation and can be used as a coefficient to represent the time course of the visual acuity changes. The equation was applied to the visual acuity for 3 years after the first visit using the least squares method, and the value of α was calculated for each eye. The mean of the rate constant α was calculated for each group shown in Table 1, and the statistical significance of the difference between each group was determined by Student's t-test with Welch's correction. Because the type of ocular inflammation, iridocyclitis or uveoretinitis can influence the visual outcome,[11] the mean value of the rate constant α was recalculated, excluding eyes with the iridocyclitis type of BD. Systemic therapy longer than 1 year was considered in the data analysis.

Results

During the 15-year period from 1974 to 1988, more than 100 new patients with BD visited our clinic in each 5-year period. In the most recent 5-year period from 1989 to 1993, the number of new patients decreased to 77 (Figure 2). During this 20-year period, the BD patients were predominantly

Figure 1. Changes of visual acuity in patients with Behçet's disease. Best-fit line determined by least squares method. Rate constant of line indicates rate of visual acuity changes in the three-year period between 1978 and 1981, and can be used as a coefficient to represent time course of visual acuity changes.
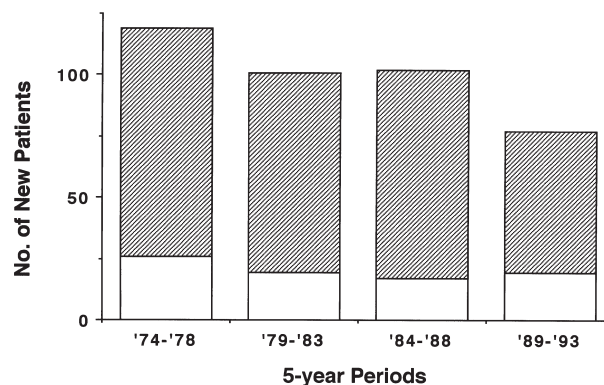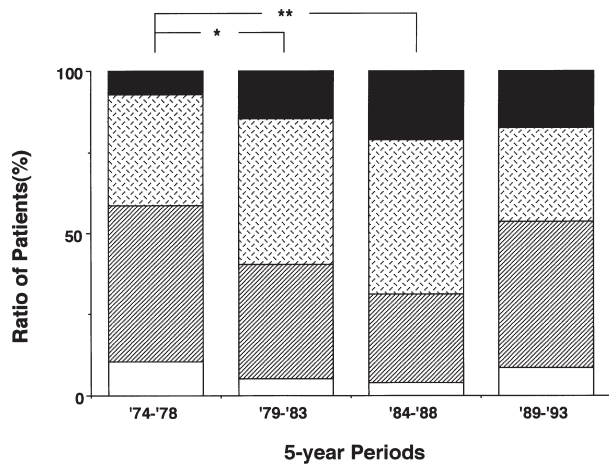

Figure 2. Number of new Behçet's disease patients in each 5-year survey group. Subjects were divided into 4 groups according to year of first visit to our clinic. □: woman, ▨: man.
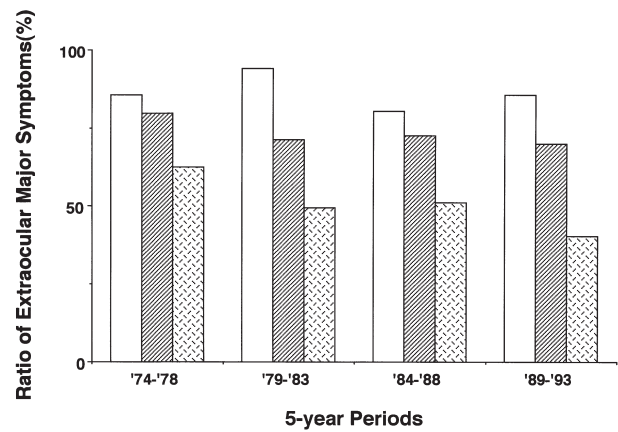
Figure 3. Age at onset. Percentage of Behçet's disease patients in each 5-year period whose onset age was under 21 (□), between 21 and 30 (▨), between 31 and 40 (▩), or over 40 (■). Mean age at onset in second and third 5-year periods was significantly older than that in first 5-year period (Student's t-test with Welch's correction). *$P < .05$, **$P < .01$.

men. The percentage of women was 21.8% (26 of 119), 18.8% (19 of 101), and 16.7% (17 of 102) for each 5-year period during the 15 years from 1974 to 1988, respectively (Figure 2). In the most recent 5-year period, the percentage of women patients increased to 24.7% (19 of 77), but there was no statistical difference between 5-year survey periods.
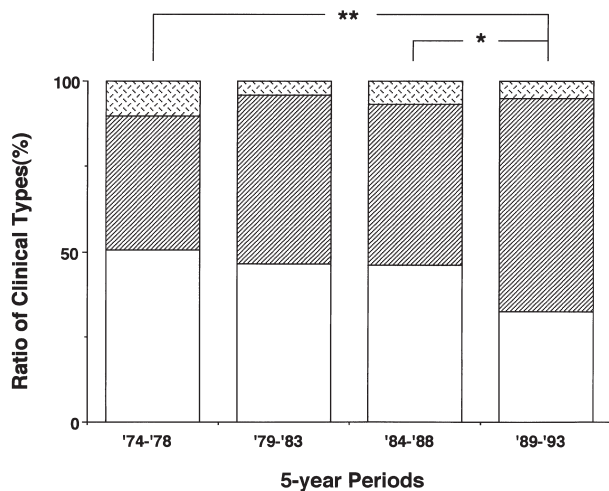

Figure 4. Clinical types. Percentage of Behçet's disease patients classified as complete type (□), incomplete type (▨), or unknown type (▩). Percentage of patients with incomplete type in recent 5-year period increased significantly compared with those in first and third 5-year periods (χ^2 test). *$P < .05$, **$P < .01$.

Figure 5. Extraocular major symptoms. Percentage of Behçet's disease patients with oral aphtha (□), skin lesions (▨), genital ulcer (▩).

The ocular symptoms were first manifested during the third or fourth decade of life in 70% of the patients. Since 1979, there has been a slight increase in the percentage of patients who had their first ocular attack in the fourth decade (Figure 3). The mean age of onset was 30.0 ± 8.1 (SD), 33.0 ± 8.6, 34.5 ± 8.7, and 31.4 ± 9.8 years for each 5-year period from 1974 to 1993. Statistical analysis showed that the difference in the age at onset was significant between the first and second 5-year periods ($P < .05$), and also between the first and third periods ($P < .01$) by t-test with Welch's correction.
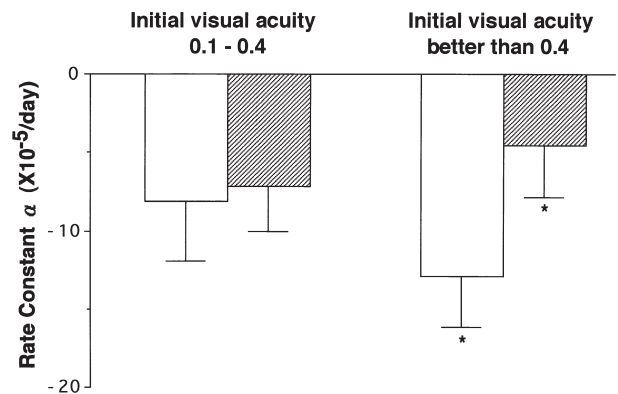
Figure 6. Visual prognosis of 122 patients (155 eyes) who were followed up for more than 3 years and whose visual acuity at first visit was 0.1 or better. Subjects were divided into 4 groups as shown in Table 1. Mean value of rate constant α in each group is shown and statistically compared by Student's t-test with Welch's correction. □: year of first visit between 1974 and 1983, ▨: year of first visit between 1984 and 1993. *$P < .05$.

Table 2. Proportion of Eyes With Iridocyclitis

Year of First Visit	Visual Acuity at First Visit	
	0.1–0.4	Better Than 0.4
1974–1983	1/32 eyes (3.1)	5/49 eyes (10.2)
1984–1993	0/35 eyes (0)	2/39 eyes (5.1)

Percents are in parentheses.

The percentage of the incomplete type of BD gradually increased during the 20-year period, from 39.5% (47 of 119) to 49.5% (50 of 101) to 47.1% (48 of 102) to 62.3% (48 of 77) for each 5-year period from 1974 to 1993 (Figure 4). Statistical analysis showed that the difference in the percentage of incomplete type was significant between the first and fourth groups ($P < .01$), and also between the third and the fourth groups ($P < .05$), by χ^2 test.

Oral aphtha and skin lesions were the most frequent extraocular major symptoms throughout the survey period. Genital ulcer was usually the least frequent sign and gradually decreased in the last 15 years (Figure 5). There was no statistically significant difference between 5-year survey period groups in the frequency of major extraocular symptoms.

The visual prognosis of the 122 patients (155 eyes) followed for more than 3 years whose visual acuity at the first visit was 0.1 or better was analyzed (Figure 6). The rate constant, α, was used to represent the

time course changes in visual acuity, with higher rate constants indicating a better visual prognosis for the group. In the groups of patients whose initial visual acuity was between 0.1 and 0.4, the mean value of α was -8.15×10^{-5} in the 1974–1983 group, and -7.16×10^{-5} in the 1984–1993 group. This difference was not statistically significant. In the groups of patients whose initial visual acuity was better than 0.4, the mean rate constant α of the 1974–1983 group was -12.91×10^{-5}, whereas that of the 1984–1993 group increased to -4.55×10^{-5}. This increase was statistically significant by Student's t-test with Welch's correction ($P < .05$). The visual prognosis was considered to be better in the 1984–1993 group than in the 1974–1983 group. Among patients with an initial visual acuity better than 0.4, the iridocyclitis type of the disease was observed in 10.2% of the 1974–1983 group and in 5.1% of the 1984–1993 group (Table 2). After excluding these eyes, the recalculated mean rate constant α was -14.36×10^{-5} for the 1974–1983 period and -5.45×10^{-5} for the 1984–1993 period. The increase was statistically significant ($P < .05$).

Analysis of the systemic medication in patients with an initial visual acuity better than 0.4 disclosed a difference between the earlier 10-year period (1974–1983) and the recent 10-year period (1984–1993). The main drug therapy consisted of colchicine and cyclophosphamide in the earlier period, and of colchicine and cyclosporin in the recent period (Table 3). The mean rate constant α was calculated in

Table 3. Type of Oral Medication[a]

Oral Medication	1974–1983[b]	
	No. of Patients	No. of Eyes
Colchicine/cyclophosphamide	14	19
Colchicine	13	17
Colchicine/cyclophosphamide/steroids	3	3
Cyclophosphamide	2	3
Colchicine/steroids	1	1
None	4	6
Total	37	49
	1984–1993[b]	
Colchicine	9	12
Ciclosporin	9	12
Colchicine/ciclosporin	3	4
Colchicine/cyclophosphamide/ciclosporin	2	3
Other combination	4	5
None	3	3
Total	30	39

[a]Oral medication for more than 1 year for patients whose initial visual acuity was better than 0.4.
[b]Year of first visit.

Table 4. Oral Medication and Visual Prognosis

Year of First Visit	Oral Medication	Number of Eyes	Mean Value of Rate Constant α
1974–1983	Colchicine/cyclophosphamide	19	-15.11×10^{-5}
	Colchicine	17	-7.16×10^{-5}
1984–1993	Colchicine	12	0.30×10^{-5}
	Ciclosporin	12	-1.96×10^{-5}

the four groups of patients for the 1974–1983 period in the colchicine and cyclophosphamide and the colchicine alone administered groups; and for the 1984–1993 period, the colchicine alone group and the ciclosporin alone group. As shown in Table 4, the visual prognosis for the latter two groups is better than for the former two.

Discussion

In this retrospective study, the number of new patients with BD was found to decrease during the most recent 5-year survey period from 1989 to 1993. This observation is similar to that of the nationwide survey report in Japan in 1992.[12] According to that survey, the estimated incidence of BD was 7.5 per million population, which represented a decrease in comparison to the 8.9 per million in the 1984 survey. A decrease in the number of patients with BD was also reported by the Hokkaido University School of Medicine, located in the northern island of Japan.[13]

The higher ratio of men/women BD patients is apparent in this study, but the ratio has decreased during the most recent 5-year period. The nationwide survey also indicated that the men/women ratio of BD patients with ocular symptoms had decreased in the complete type and showed no change in the incomplete type.[12]

The age of disease onset was between 21 and 40 years in more than 70% of the patients, as usually described for BD. However, the number of patients who manifested the first ocular attack at the age of 40 or older has increased slightly over the last 15 years. The nationwide survey also showed that the mean age of disease onset has become higher in recent years.[12]

In this study, the proportion of the incomplete type of Behçet's disease has increased recently, as was found in the nationwide survey.[12] In the survey at Hokkaido University, the ratio of men patients with the incomplete type also increased.[13] Among the extraocular major symptoms, oral aphtha and skin lesion were frequent, but genital ulcer has be-

come less common over the last 20 years. The gradual decrease in frequency of genital ulcer may explain the increase in the incomplete type, as suggested by Kotake et al.[13]

We evaluated the visual prognosis for patients with BD by the least squares method. In the patients whose initial visual acuity was better than 0.4, the visual prognosis was significantly better among those who visited our clinic between 1984 and 1993 than in the group between 1974 and 1983. Even after excluding those eyes with the iridocyclitis type of disease, the difference was still significant in the recalculated mean rate constant α between these two groups. The number of eyes categorized as the iridocyclitis type is very small and the type of ocular inflammation had no influence on the total evaluation of visual prognosis. Kotake et al[13] reported that the visual prognosis of BD patients improved despite the increase in the ratio of patients with uveoretinitis type, which is considered a more severe eye finding than iridocyclitis. They suggested that the improvement in visual prognosis was due to the more effective treatment with ciclosporin. In our clinic, ciclosporin has been administered to BD patients with refractory uveitis since 1985, when the efficacy of ciclosporin was first reported by Nussenblatt et al.[14] In our institution, the main drugs of choice for the treatment of ocular inflammation in BD patients were colchicine and cyclophosphamide in the 1974–1983 period, and colchicine and ciclosporin in the 1984–1993 period. Our data agree with the conclusion by Kotake et al[13] that ciclosporin has contributed significantly to improved visual prognosis for BD. However, it is difficult to conclude from this retrospective study that ciclosporin is the sole factor for improvement of visual prognosis. A tendency to milder symptoms in BD patients has been suggested in the nationwide survey, which showed an increase in patients with no ocular attack or amelioration, a decrease in those with deterioration, and a decreasing proportion of deaths. The improvement in visual prognosis demonstrated in this study may depend partly on the general tendency toward mild BD in Japan. We evaluated the visual prog-

nosis of BD patients in the data obtained from a 3-year follow-up in our clinic. However, a longer follow-up study is needed to establish the effect of medication on the visual prognosis for patients with BD.

References

1. Furudate N, Kotake S, Sasamoto Y, et al. Incidence of uveitis at Hokkaido University Hospital. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1237–41.

2. Konno Y, Numaga J, Fujino Y, Joko S, Masuda K. Incidence of uveitis at Tokyo University Hospital. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1243–7.

3. Sugita M, Nakamura S, Enomoto Y, Yamamoto T, Ohno S. Epidemiological study on endogenous uveitis. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1249–52.

4. Nakagawa Y, Tada R, Fuji S, et al. Changing trends of uveitis during the past twenty-two years. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1257–61.

5. Kogiso M, Tanouchi Y, Bando Y, Mimura Y. Incidence of endogenous uveitis at Tokushima University Hospital. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1263–6.

6. Ikeda E, Wada K, Yoshimura K, Mochizuki M. Statistics of uveitis in northern and southern districts in Kyushu. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1267–70.

7. Mizushima Y. Recent research into Behçet's disease in Japan. Int J Tissue React 1988;10:59–65.

8. Mimura Y. Immunological and clinical studies on ocular allergic diseases. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1979;83:1909–75.

9. Miyaura T, Wakano I, Mimura Y. Changes in ocular manifestations of Behçet's disease. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1982;33:987–91.

10. Hijikata K, Masuda K. Visual prognosis in Behçet's disease: effects of cyclophosphamide and colchicine. Jpn J Ophthalmol 1978;22:506–19.

11. Mishima S, Masuda K, Izawa Y, Mochizuki M, Namba K. Behçet's disease in Japan: ophthalmologic aspects. Trans Am Ophthalmol Soc 1979;LXXVII:225–79.

12. Nakae K, Masaki F, Hashimoto T, Inaba G, Mochizuki M, Sakane T. Recent epidemiological features of Behçet's disease in Japan. In: Inaba G, ed. Behçet's disease. New York: Elsevier Science, 1993:145–51.

13. Kotake S, Furudate N, Sasamoto Y, et al. Clinical study on patients with Behçet's disease in Hokkaido. Ocular Immunol Inflamm 1995;3:237–41.

14. Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancey K. Effectiveness of cyclosporin therapy for Behçet's disease. Arthritis Rheum 1985;28:671–9.