The Clinical Features of Behçet’s Disease in Yongdong Districts: Analysis of a Cohort Followed from 1997 to 2001

This study was undertaken to evaluate the clinical features of a cohort of Behçet’s disease (BD) followed up from January 1997 to July 2001 in Yongdong districts in Korea, and to compare the results with the literature. Overall features of clinical manifestations were similar to those described in the literature. However, the frequency of gastrointestinal (GI) ulcerations was much higher than those of other Korean studies. The Korean studies including ours revealed a lower frequency of vascular lesions and epididymitis compared with studies of other countries. The most common site and pattern of inflammatory arthritis were knees and monarticular involvement, respectively. In addition, in most patients, the ocular lesions involved the posterior uveal tract, and the terminal ileum and cecum were the most common sites of GI involvement. Patients with ocular lesions or GI lesions showed a good prognosis during the follow-up. The HLA-B51 antigen was positive in 50.7% of patients, and it was more commonly found in patients with a familial BD.

Key Words : Behçet’s Syndrome; Eye Manifestations; Oral Manifestations; Skin Manifestations; Korea

INTRODUCTION

Behçet’s disease (BD) is a chronic inflammatory disorder involving multiple organs such as oral ulcerations, genital ulcerations, uveitis, and skin lesions. It may also involve other organs, including joints, heart, lungs, central nervous system, and gastrointestinal tract. Although the main pathology of BD has been known to be the underlying vasculitis, the exact etiopathogenesis is still unknown. Patients with BD have clustered in the ethnic area adjacent to the ancient Silk Road that extends from the eastern Asia to the Mediterranean basin (1, 2). Some clinical features of this disease, including the prevalence of HLA-B51, ileocecal ulcerations, and a positive pathergy reaction, as well as a sexual predisposition to the disease, have been described to be different according to the geographical areas (2, 3). Moreover, regional differences in the prevalence of the disease within a country have been reported from Japan, which could be due to the ethnic or geographic factors (4).

In Korea, information for the clinical features of BD in a confined geographical region has been limited. Therefore, this study was undertaken to evaluate the clinical characteristics of a cohort of BD followed-up in a university medical center at Yongdong districts (eastern coastal region of Kangwon Province, Korea), and to compare the results with those of the literature.

MATERIALS AND METHODS

During period from January 1997 thru July 2001, 73 patients with BD who satisfied the criteria by International Study Group (ISG) (5) were prospectively analyzed. The demographic features of patients were as follows: 25 male and 48 female patients; mean age at onset (± SD), 35.2 ± 8.9 yr; mean age at presentation (± SD), 39.5 ± 10.2 yr; mean duration of Behçet’s disease, 5.6 yr (range 6 months to 40 yr); mean period of the follow-up, 18.2 months (range 3 months to 54 months). The age at onset was defined as the first time the patient fulfilled the ISG criteria. The presence, absence, and characteristics of each clinical manifestation were assessed by a rheumatologist. The patients were evaluated by an ophthalmologist, initially and whenever the ocular symptoms or signs were encountered, and by specialists of related symptoms whenever clinically indicated along the course of the disease. The inflammatory arthritis was defined as the presence of any episode of either swelling, redness, or heating of the involved joints that was confirmed by a rheumatologist.

The pathergy reaction was performed as described elsewhere in all patients with BD (6). Briefly, intradermal prick with a 21-gauge disposable needle was done under sterile condition, and the results were read at 48 hr by the same physician. The formation of a papule or pustule was considered a positive reaction. In addition, it was retested in a few BD patients with initially negative reaction whose the disease flared up during...
the follow-up. If the results were positive, they were also considered to have a positive reaction. In addition, HLA-B51 was tested by a two-step polymerase chain reaction with sequencespecific primers in all patients with BD (7, 8).

The data were entered onto a computer database, and analyzed by the SPSS statistical program version 10.0 for Windows (SPSS Inc., Chicago, IL, U.S.A.). The statistical significance was evaluated by Fisher’s exact test. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

There was a female predominance, with a male-to-female ratio of 1:1.92. The mean ages at onset in male and female patients were 34.2±9.1 yr and 35.8±8.9 yr, respectively, indicating no gender difference. The disease was most commonly in the thirties (41.1%), followed by twenties (30.1%) and forties (20.5%). There were no patients under the age of 20 or over the age of 60 yr (Table 1).

The prevalence of clinical features in patients with BD is presented in Table 2. Oral ulcerations were found in 100% of patients, genital ulcerations in 75.3%, papulopustular eruption or pseudofolliculitis in 57.5%, erythema nodosum-like lesions in 52.1%, positive pathergy reaction in 34.2%, peripheral arthritis in 24.7%, ocular lesions in 23.3%, gastrointestinal ulcerations in 15.1%, vascular lesions in 5.5%, central nervous system lesions in 4.1%, epididymitis in 1.4%, and pulmonary involvement in 1.4%.

Recurrent oral ulcerations were the initial manifestation of the disease in 63 patients (86.3%), followed by genital ulcerations in 4 patients (5.5%), skin lesions in 3 patients (4.1%), ocular lesions in 2 patients (2.7%), and arthritis in 1 patient (1.4%). The sites of genital ulcerations in 56 patients are depicted in Table 3. The vulva was the most common site for female patients and scrotum for male patients. In addition, the prevalence of skin lesions was different according to the gender (Table 4). The more common skin lesions in male and female patients were papulopustular eruption or pseudofolliculitis and erythema nodosum-like lesions, respectively.

The characteristics of inflammatory arthritis are depicted in Table 5. The most common site of this lesion was the knees followed by ankles and wrists. In 18 patients with inflammatory arthritis, the mean frequency of arthritis attack was 2.4
The pattern of ocular involvement in 17 patients is shown in Table 6. The most common pattern of arthritis was monoarticular and asymmetric involvement. Radiographic sacroiliitis was found in 5 patients (6.8%), in whom 3 patients (4.1%) concurrently fulfilled the criteria of spondyloarthropathy by the European Spondyloarthropathy Study Group (ESSG) (9) as well as the ISG criteria. The enthesitis was observed in 5 patients (6.8%), in whom 3 patients also met the ESSG criteria (10). In addition, there were 2 patients with osteonecrosis or bone infarction, in whom one patient developed bone infarction without the use of corticosteroids and the other had a past history of significant corticosteroids administration to treat the serious complications of BD (11).

The patterns of ocular involvement in 17 patients are presented in Table 6. In most patients, the posterior uveal track was involved except 4 patients, of whom 3 had only an anterior uveitis and one patient with a nodular scleritis, described previously (12). The frequency of ocular involvement in male and female patients was 28.0% and 20.8%, respectively, indicating no gender difference (p=0.492). In addition, there have been no patients who lost their vision from the ocular lesions of BD during the follow-up with the exception of one patient who had already lost his vision of left eye at presentation.

Table 7 shows the sites of gastrointestinal ulcerations in 11 patients. The terminal ileum or cecum was more commonly involved. Four of these patients had undergone the surgical procedures due to the bleeding or perforation from the intestinal ulceration at presentation. However, no patients received the surgical treatment during the follow-up period. In addition, three (27.3%) of patients with intestinal ulcerations had a past history of erroneous diagnosis with an appendectomy. As for the pathergy reaction, the male patients showed a higher positive rate (44.0%) than the female patients (29.2%), however, there was no statistical significance (p=0.299) (Table 8).

The HLA-B51 antigen was positive in 37 (50.7%) of 73 patients. In addition, there were 3 families in which 8 patients (11.0%) were affected by BD, and this antigen was positive in 7 (87.5%) of these patients.

### DISCUSSION

The comparative data of clinical features of BD in Korea, Turkey, Germany, and Greece are presented in Table 9 (3, 13-17). Because the criteria for the clinical studies of BD in Korea have not been unified, it is difficult to compare our data with others in the literature. Whereas we employed the ISG criteria, other authors adopted the criteria by the Behcet’s Disease Research Committee of Japan (Japanese criteria) (18, 19) in which some authors comprised incomplete type and others suspected type or possible type. The Korean studies including ours showed the female predominance of patients, and this was also the case in Japan and the United States. However, males were more frequently affected in Germany, Greece, and the Middle Eastern countries (2, 3). Whereas the age at onset in the current study and in a multicenter study in Korea (13) was older when compared with that in other countries, another study in Korea (15) showed an earlier onset which might be partly due to the criteria adopted to embrace the possible type. In addition, the prevalence of vascular involvement and epididymitis in Korean studies including ours showed the female predominance of patients, and this was also the case in Japan and the United States.

### Table 6. The pattern of ocular involvement in 17 patients

| Pattern                                      | No. of patients (%) |
|----------------------------------------------|---------------------|
| Anterior and posterior uveitis               | 8 (47.1)            |
| Posterior uveitis                            | 3 (17.6)            |
| Anterior uveitis                             | 3 (17.6)            |
| Posterior uveitis and retinal vasculitis     | 2 (11.8)            |
| Scleritis                                    | 1 (1.4)             |

### Table 7. The sites of gastrointestinal ulcerations in 11 patients

| Site                        | No. of patients |
|-----------------------------|-----------------|
| Terminal ileum              | 9               |
| Cecum                       | 5               |
| Ascending colon             | 2               |
| Transverse colon            | 2               |
| Esophagus                   | 2               |

### Table 8. The results of pathergy reaction in 25 patients

| Male                        | Female          |
|-----------------------------|-----------------|
| No. of patients with positive pathergy reaction (%) | No. of patients with negative pathergy reaction (%) |
| 11 (44.0)                   | 14 (56.0)       |
| 14 (29.2)                   | 34 (70.8)       |

during the follow-up. The most common pattern of arthritis was monoarticular and asymmetric involvement. Radiographic sacroiliitis was found in 5 patients (6.8%), in whom 3 patients (4.1%) concurrently fulfilled the criteria of spondyloarthropathy by the European Spondyloarthropathy Study Group (ESSG) (9) as well as the ISG criteria. The enthesitis was observed in 5 patients (6.8%), in whom 3 patients also met the ESSG criteria (10). In addition, there were 2 patients with osteonecrosis or bone infarction, in whom one patient developed bone infarction without the use of corticosteroids and the other had a past history of significant corticosteroids administration to treat the serious complications of BD (11).

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### Table 9. The clinical features of Behcet’s disease in Korea, Turkey, Germany, and Greece

| Clinical features                      | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---------------------------------------|---|---|---|---|---|---|---|
| Oral ulcers as initial symptom (%)    | 86.3 | NA | NA | 78.5 | 86.5 | 66.0 | 64.0 |
| Mean age at onset (yr)                | 35.2 | 33.0 | NA | 20S | 26.5 | 25.0 | NA |
| Oral ulcers (%)                       | 100 | 98.8 | 100 | 97.5 | 100 | 99 | 100 |
| Genital ulcers (%)                    | 75.3 | 83.2 | 71.1 | 56.7 | 88.2 | 74.5 | 78.0 |
| EN-like lesions (%)                   | 52.1 | 84.3 | NA | 55.3 | 47.6 | 37.0 | NC |
| Pseudofolliculitis (%)                | 57.5 | 29.7 | NA | 54.2 | 50.8 | NC | |
| Positive pathergy (%)                 | 34.2 | 15.4 | 47.3 | NA | 56.8 | 51.8 | 30.0 |
| Arthritis (%)                         | 24.7 | 38.4 | NA | 24.2 | 6.7 | 59 | 48 |
| Ocular lesions (%)                    | 23.3 | 50.9 | 30.7 | 28.5 | 28.9 | 58.9 | 75.0 |
| GI lesions (%)                        | 15.1 | 7.3 | 5.3 | 4.0 | 2.8 | 15.8 | 3.0 |
| Vascular lesions (%)                  | 5.5 | 1.8 | 10.5 | NA | 16.8 | 25.1 | 8.0 |
| CNS lesions (%)                       | 4.1 | 4.6 | 3.5 | 5.7 | 2.2 | 12.8 | 20.0 |
| Epididymitis (%)                      | 1.4 | 0.6 | 1.8 | NA | 15.9 | 17.0 | |

1. the current study; 2. Bang et al. (multicenter study) (13); 3. Eun et al. (14); 4. Bang et al. (15); 5. Gürler et al. (Turkish study) (16); 6. Zouboulis et al. (German study) (17); 7. Kaklamanis et al. (Greece study) (3). NA, not available; NC, not clearly described; *EN, erythema nodosum; **, described as skin lesions; PPL, papulopustular lesions.
ours was lower than that in other countries. However, the overall features of clinical manifestations were similar to those in the literature (3).

Although most clinical manifestations in the present study were in line with other Korean studies, some clinical features were somewhat different. Eun et al. described the highest rate of a positive pathergy reaction (14), and this might be related with the needle used in the pre-AIDS-era. After the introduction of a disposable needle, the prevalence and intensity of a positive pathergy reaction have been described to decrease when compared with those by the non-disposable needle used in the pre-AIDS era (20). The current study showed a somewhat higher rate of a positive pathergy reaction than the multicenter study in Korea (13). We previously reported that the positive pathergy reaction was usually found in the active phase of the disease in individual cases with a positive reaction (6). In the current study, the pathergy reaction was also done in the relatively active stage of BD during the follow-up, and this might be one reason for the somewhat higher rate of the positive pathergy reaction. On the other hand, the information about the relationship between the pathergy reaction and gender of patients with BD has been limited. Yazici et al. described that even though the prevalence of the pathergy reaction was not different according to gender, male patients had a stronger reaction (21). However, the positive pathergy reaction was more commonly encountered in male patients in the current study and in the multicenter study in Korea (13), although there was no statistical significance in our study. In addition, because the strong reaction such as a pustule formation was very rare as demonstrated in our previous report (6), the difference of the intensity of this reaction between male and female patients could not be assessed.

The uveitis of BD involves both anterior and posterior uveal tracts and causes the loss of sight in 25% of patients (3, 22). In the present study, the most common pattern of ocular lesions was the involvement of both the anterior and posterior tracts. We used a therapeutic regimen, which consisted of cyclosporine (5 mg/kg/day) for first 6 months, followed by azathioprine (1-2 mg/kg/day) for 18 months. Prednisolone (PD) (1 mg/kg/day) was initially given and was tapered to 5 mg/day within one month. Colchicine (1.2 mg/day) was also prescribed. Cyclophosphamide (1-2 mg/kg/day) was given together to patients with an active vasculitis for 3 to 6 months.

The ulcerative lesions of the intestinal BD are diverse from small shallow ulcerations to large and deep penetrating ulcerations liable to perforate. Moreover, postoperative recurrence and complications are relatively frequent (26, 27). In the present study, no patients with intestinal BD received the surgical treatment due to the complications of intestinal ulcerations during the follow-up. So, our therapeutic regimens appeared to be effective for patients with the active intestinal ulcerations or patients undergone the surgery due to the complicated ulcerations. Some patients with ileocecal ulcerations could be misdiagnosed as appendicitis because of their location. Lee et al. reported 6 patients (23.1%) who were misdiagnosed as appendicitis before operation (26). We experienced 3 such patients (27.3%).

Yurdakul et al. described that the attacks of arthritis in BD were mostly monoarticular (68%), and knees, ankles, and wrists were the most commonly involved joints (28). Our study revealed very similar results. The prevalence of inflammatory arthritis in our study was comparable to those of other Korean studies. However, Kim et al. described that the frequency of arthropathy was 70.2% and the most common pattern of involvement was oligoarticular (29). Such a high frequency of the joint involvement might be speculated because they used the questionnaire to obtain the information of joint symptoms, and also employed a broad concept “arthropathy” rather than the inflammatory arthritis.

The HLA-B51 antigen has been a well-known genetic factor associated with BD, and has appeared to be higher in countries adjacent to the ancient Silk Road (1). Lee et al. described that the frequency of HLA-B51 in patients with BD was 44.2% in 1988 (30). The odd ratio for the development of BD in Korean with HLA-B51 in another Korean study was 6.8 (95% confidence interval; 3.0-15.3), and patients with this antigen tended to manifest uveitis, erythema nodosum, and the full-blown syndrome as complete BD (8). HLA-B51 in the present study was positive in 50.7% of BD patients. On the other hand, familial BD was described in 13.4% of patients with
BD in one Korean study (31), and the positive family history was documented in 8 patients (11%) in the current study. In addition, the occurrence of BD in a family of which 4 siblings were affected could not be explained by any specific HLA phenotype (32). Nishimura et al. reported that the prevalence of HLA-B51 in patients with a familial BD was 92% (33). It was 87.5% in the present study. Therefore, the HLA-B51 antigen was more commonly found in patients with a familial BD than in patients without a family history of BD.

This is the first clinical study of BD in a confined area of Korea. Some clinical features have been well known to be different according to the ethnic areas, and regional differences within a country have also been reported. We hope that the clinical feature of BD in other areas of this country will be reported and the criteria for the clinical studies of BD will be unified to easily compare to each other.

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