



# Clinical phenotypes of Korean patients with Behcet disease according to gender, age at onset, and HLA-B51

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**Background/Aims:** The clinical manifestations of Behcet disease (BD) have been reported to differ according to country, region, and race. Gender, onset age, and human leukocyte antigen (HLA)-B51 have also been known as the factors that influence the clinical features of BD. The aim of this study is to investigate the clinical phenotypes of Korean patients who visited the rheumatology clinic with BD with respect to gender, onset age, and HLA-B51.

**Methods:** Total 193 Korean patients (129 females and 64 males) fulfilling the international criteria for BD were retrospectively assessed.

**Results:** The mean age at disease onset and disease duration of the BD patients were  $32.2 \pm 11.1$  and  $14.2 \pm 9.3$  years, retrospectively. Females suffered more frequently from genital ulcers (90.7% vs. 75.0%,  $p < 0.01$ ), peripheral arthritis (67.4% vs. 43.8%,  $p < 0.01$ ), and inflammatory low back pain (38.8% vs. 23.4%,  $p = 0.03$ ) than males, while skin involvement was more frequent in males than in females (90.6% vs. 75.2%,  $p = 0.01$ ). The patients with late onset of BD ( $> 40$  years) suffered from neurologic involvement (15.9% vs. 4.2%,  $p = 0.007$ ) more frequently than those with early onset of BD. The patients with HLA-B51 showed earlier onset of disease than without HLA-B51 ( $28.3 \pm 11.4$  years vs.  $33.8 \pm 11.6$  years,  $p = 0.02$ ) and the neurologic and gastrointestinal involvements were more frequent in the patients without HLA-B51 than with HLA-B51 (17.2% vs. 2.5%,  $p = 0.02$  and 20.7% vs. 2.5%,  $p = 0.01$ , respectively).

**Conclusions:** The clinical phenotypes in Korean patients with BD may be influenced by gender, onset age and HLA-B51.

**Keywords:** Behcet syndrome; Gender identity; Age of onset; HLA-B51 antigen

## INTRODUCTION

Behcet disease (BD) is a chronic inflammatory disease that has recurrent oral and genital ulcers as a prominent feature, but can involve almost all organs, including the skin, eyes, gastrointestinal tract, joints, cardiovascular system, and nervous system [1]. Although the prevalence is highest in East Asian countries, the Middle East and

the Eastern Mediterranean area, BD can be found in any country due to immigration [2,3].

The etiology of BD is uncertain, but genetic such as human leukocyte antigen (HLA)-B51, environmental, microbiological and immunological factors have been proposed to be related with BD [4]. According to the country, clinical manifestations have been reported to differ according to country, region, and race [5-7]. Oc-

ular manifestations develop in 35% to 92% of cases and gastrointestinal manifestations in 3.3% to 37%, and central nervous system involvement occurs in 0% to 44% of cases [5]. In Israel, Arab patients have more severe eye disease than Jewish patients and the Druse have milder ocular and neurologic involvement than Arabs [6,7]. Demographic factors including gender [8-12] and age at onset [13-19] or genetic factors such as HLA-B51 [20-23] have also been reported to influence the clinical manifestations of BD. However, the reported results varied countries, regions, and races [8-23]. Thus we assume that multiple factors including race, region, country, gender, and genetics could influence clinical manifestations in a complex manner.

There were not many studies about the influence of demographic and genetic factors on clinical phenotypes of BD although they used different diagnostic criteria. Especially, Korean data on the basis of rheumatology clinics were lacking. The aim of this study is to investigate the clinical phenotypes of Korean patients who visited the rheumatology clinic with BD according to demographic and genetic factors. To do this we selected gender, age at onset, and HLA-B51 status as influence factors that were suggested by previous reports.

## METHODS

We retrospectively reviewed the medical records of 193 BD patients who consecutively visited our rheumatology clinic. All of them fulfilled the international criteria for BD (ICBD) [24]. The study protocol was approved by Institutional Review Board of Gachon University Gil Medical Center and informed consent was waived from all patients by the Board (GCIRB2971-2012).

Clinical and laboratory findings were obtained from the medical records. Ocular lesions were diagnosed by the ophthalmologist. We defined joint involvement as joint swelling or pain with swelling of the joint or articular damage on simple radiography. Inflammatory back pain (IBP) was evaluated according to the criteria of Assessment of SpondyloArthritis international Society (ASAS) experts [25]. Vascular manifestations included venous thrombophlebitis, arteritis and superficial phlebitis that were confirmed by Doppler sonography or angiography. Neurologic involvement (Neuro-BD) was diagnosed

by international consensus recommendation criteria for Neuro-BD diagnosis and included the definite neuro-BD and the probable neuro-BD [26]. Gastrointestinal involvement was defined as confirmed with gastroduodenoscopy or colonoscopy by gastroenterologists.

We defined the onset of BD as the age of the patient when the initial manifestation of BD presented. The duration of BD was calculated as the time interval between the onset of BD and the age at the last visit of the patient to our clinic. Onset age could be informed from 188 patients and HLA-B51 was tested for in 98 patients. Major organ involvement was defined as involvement of the eyes, nervous system, gastrointestinal tract or vessels.

The comparisons of the clinical manifestations according to gender, onset age, and HLA-B51 status were performed using the chi-square test, Fisher exact test, or Student *t* test. Statistical calculations were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A value of  $p < 0.05$  was considered to indicate statistical significance.

## RESULTS

Of the 193 BD patients, 129 (66.8%) were female and 64 (33.2%) were male. The male to female ratio was 0.5:1. The mean ages ( $\pm$  SD) at disease onset and at enrollment of patients with BD were  $32.2 \pm 11.1$  and  $44.7 \pm 11.1$  years, respectively. The mean disease duration of BD was  $14.2 \pm 9.3$  years (Table 1).

The oral ulcer was the most common manifestation, followed by genital ulcers, skin involvement, peripheral arthritis, major organ involvement, and IBP (Table 1). The number of patients with major organ involvement increased over time. In 32 patients (16.6%), BD presented with major organ involvement; uveitis (13%), gastrointestinal involvement (5.2%), vascular involvement (3.1%), and neurologic involvement (1%). And total 76 patients (39.4%) experienced the major organ involvements for their disease duration. The frequencies of all types of major organ involvement, with the exception of vascular involvement, increased more than 2-fold during the course of BD compared to the onset of BD. Thirty-one of 105 BD patients (29.5%) who were performed the pathergy test showed positive reaction. HLA-B51 was present in 40 of 98 patients (40.8%).

**Table 1. Clinical manifestations of Behcet disease according to gender**

Clinical feature	Total (n = 193)	Female (n = 129)	Male (n = 64)	p value
Age, yr	44.7 ± 11.1	44.6 ± 10.4	44.7 ± 12.5	NS
Onset age, yr	32.2 ± 11.1	31.5 ± 10.7	33.8 ± 11.8	NS
Disease duration, yr	14.2 ± 9.3	15.0 ± 9.8	12.4 ± 7.9	NS
Follow-up duration, yr	4.7 ± 3.8	4.5 ± 3.6	5.1 ± 4.0	NS
Positive HLA-B51 (performed in 98 patients)	40 (40.8)	28 (43.1)	12 (36.4)	NS
Positive pathergy test (performed in 105 patients)	31 (29.5)	18 (25.7)	13 (37.1)	NS
Oral ulcer	191 (99.0)	127 (98.4)	64 (100.0)	NS
Genital ulcer	165 (85.5)	117 (90.7)	48 (75.0)	< 0.01
Skin lesion	155 (80.3)	97 (75.2)	58 (90.6)	0.01
Pseudofolliculitis	87 (45.1)	50 (38.8)	37 (57.8)	0.01
Erythema nodosum	102 (52.8)	64 (49.6)	38 (59.4)	NS
Joint involvements	122 (63.2)	91 (70.5)	31 (48.4)	< 0.01
Arm	71 (33.0)	56 (43.4)	15 (23.4)	< 0.01
Leg	90 (46.6)	65 (50.4)	25 (39.1)	NS
Shoulder	21 (10.9)	18 (14.0)	3 (4.7)	NS
Hip	6 (3.1)	5 (3.9)	1 (1.6)	NS
Inflammatory back pain	65 (33.7)	50 (38.8)	15 (23.4)	0.03
Major organ involvement	76 (39.4)	49 (38.0)	27 (42.2)	NS
Uveitis	52 (26.9)	31 (24.0)	21 (32.8)	NS
Neurologic	13 (6.7)	8 (6.2)	5 (7.8)	NS
Gastrointestinal	22 (11.4)	16 (12.4)	6 (9.4)	NS
Vascular	8 (4.1)	3 (2.3)	5 (7.8)	NS

Values are presented as mean ± SD or number (%).  
NS, not significant; HLA, human leukocyte antigen.

### Clinical manifestations according to gender

The mean age at onset and the mean disease duration were not different according to gender. And HLA-B51 status and the positivity of pathergy test were similar in both genders. Genital ulcers, peripheral joint involvement, and IBP were more common in females, while skin lesions were more frequent in males. The differences in the frequencies of major organ involvements between genders were not statistically significant (Table 1).

### Clinical manifestations according to age at onset

There were no differences of clinical features according to age at onset except neurologic involvement (Table 2).

### Clinical manifestations according to the status of HLA-B51

The patients with HLA-B51 showed significantly earlier

onset than without HLA-B51. Pseudofolliculitis was more frequent in the patients with HLA-B51, while major organ, including gastrointestinal and neurologic, involvements were more prevalent in the patients without HLA-B51 than with HLA-B51 (Table 3).

## DISCUSSION

There are limited data about the influences of gender, age at onset, and HLA-B51 on the clinical manifestations of BD. They have been differently reported among countries and regions. It may be attributed to the variable diagnostic criteria for BD that were applied, as well as racial and national differences. Oral ulcer is an obligatory manifestation for BD diagnosis by the diagnostic criteria of the International Study Group (ISG) [27],

**Table 2. Clinical manifestations of Behcet disease according to onset of age**

Clinical feature	Total (n = 188)	≤ 40 Years (n = 144)	> 40 Years (n = 44)	p value
Age, yr	44.6 ± 10.9	40.9 ± 9.0	56.7 ± 7.4	< 0.00
Onset age, yr	32.2 ± 11.1	27.7 ± 7.8	47.2 ± 6.0	< 0.00
Disease duration, yr	14.2 ± 9.3	14.9 ± 9.6	11.8 ± 7.9	NS
Follow-up duration, yr	4.7 ± 3.7	4.3 ± 3.6	5.9 ± 3.9	0.01
Positive HLA-B51 (performed in 96 patients)	39 (40.6)	32 (45.1)	7 (28.0)	NS
Positive pathergy test (performed in 103 patients)	30 (29.1)	23 (28.0)	7 (33.3)	NS
Oral ulcer	186 (98.9)	143 (99.3)	43 (97.7)	NS
Genital ulcer	160 (85.1)	125 (86.8)	35 (79.5)	NS
Skin lesion	151 (80.3)	117 (81.3)	34 (77.3)	NS
Pseudofolliculitis	85 (45.2)	67 (46.5)	18 (40.9)	NS
Erythema nodosum	99 (52.7)	78 (54.2)	21 (47.7)	NS
Joint involvements	120 (63.8)	93 (64.6)	27 (61.4)	NS
Arm	69 (36.7)	56 (38.9)	13 (29.5)	NS
Leg	88 (46.8)	69 (47.9)	19 (43.2)	NS
Shoulder	21 (11.2)	18 (12.5)	3 (6.8)	NS
Hip	6 (3.2)	3 (2.1)	3 (6.8)	NS
Inflammatory back pain	64 (34.0)	49 (34.0)	15 (34.1)	NS
Major organ involvement	75 (39.9)	55 (38.2)	20 (45.5)	NS
Uveitis	52 (27.7)	40 (27.8)	12 (27.3)	NS
Neurologic	11 (11.2)	6 (4.2)	7 (15.9)	0.007
Gastrointestinal	21 (11.2)	14 (9.7)	7 (15.9)	NS
Vascular	8 (4.3)	5 (3.5)	3 (6.8)	NS

Values are presented as mean ± SD or number (%).  
NS, not significant; HLA, human leukocyte antigen.

which can exclude BD patients without oral ulcers. The diagnostic criteria of the Research Committee of Japan (RCJ) place great emphasis on ocular involvement [28], although it may include patients with ocular lesions associated with other diseases such as spondyloarthritis. The sensitivity and specificity of the criteria for BD have been reported to be 79.8% and 98.3% by ISG criteria, 85.3% and 97.1% by RCJ criteria and 70.7% and 97.6% by O’Duffy’s criteria, respectively [29]. ICBD was recently developed and showed increased sensitivity and accuracy by 20.1% and 11.8%, respectively compared with ISG criteria [30]. We studied the patients with BD who visited the rheumatology clinic and met the ICBD criteria. While majority of previous studies were analyzed by a specific single parameter, we investigated the comprehensive effects of multiple factors including gender, age at onset, and HLA-B51 on the clinical phenotypes of BD.

In contrast to a previous Korean study showing that skin disease was dominant in females and uveitis was dominant in males [8], we found that skin disease was dominant in males and the frequency of uveitis was not different in both genders. These differing results could be explained by the different diagnostic criteria of BD as the previous study used ISG or RCJ criteria and our study did ICBD. Moreover there could be the difference of patients’ characteristics according to the clinic where these studies were performed (dermatologic clinic in the previous study vs. rheumatologic clinic in our study). Actually the previous Korean study that performed in dermatologic clinic showed lesser frequent involvements of internal organs (gastrointestinal involvement 3.2%, neurologic involvement 1.5%, and vascular involvement 1.7%) compared with our study [8]. Our data on the basis of rheumatology clinic could encompass BD patients

**Table 3. Clinical manifestations of Behcet disease according to HLA-B51 positivity**

Clinical feature	Total (n = 98)	Positive HLA-B51 (n = 40)	Negative HLA-B51 (n = 58)	p value
Age, yr	44.8 ± 10.9	43.4 ± 10.5	45.9 ± 11.1	NS
Onset age, yr	31.6 ± 11.8	28.3 ± 11.4	33.8 ± 11.6	0.02
Disease duration, yr	13.7 ± 9.0	16.0 ± 10.5	12.1 ± 7.6	0.04
Follow-up duration, yr	4.8 ± 3.2	4.3 ± 3.2	5.1 ± 3.3	NS
Positive pathergy test (performed in 66 patients)	19 (28.8)	8 (28.6)	11 (16.7)	NS
Oral ulcer	96 (98.0)	40 (100.0)	56 (96.6)	NS
Genital ulcer	80 (81.6)	33 (82.5)	47 (81.0)	NS
Skin lesion	85 (86.7)	36 (90.0)	49 (84.5)	NS
Pseudofolliculitis	44 (44.9)	23 (57.5)	21 (36.2)	0.04
Erythema nodosum	53 (54.1)	18 (45.0)	35 (60.3)	NS
Joint involvements	52 (53.1)	19 (47.5)	33 (56.9)	NS
Arm	32 (32.7)	12 (30.0)	20 (34.5)	NS
Leg	36 (36.7)	13 (32.5)	23 (39.7)	NS
Shoulder	11 (11.2)	2 (5.0)	9 (15.5)	NS
Hip	2 (2.0)	0	2 (3.4)	NS
Inflammatory back pain	22 (22.4)	6 (15.0)	16 (29.6)	NS
Major organ involvement	41 (41.8)	11 (27.5)	30 (51.7)	0.02
Uveitis	25 (25.5)	9 (22.5)	16 (27.6)	NS
Neurologic	11 (11.2)	1 (2.5)	10 (17.2)	0.02
Gastrointestinal	13 (13.3)	1 (2.5)	12 (20.7)	0.01
Vascular	7 (7.1)	1 (2.5)	6 (10.7)	NS

Values are presented as mean ± SD or number (%).

HLA, human leukocyte antigen; NS, not significant.

with much more diverse clinical features compared the dermatology clinic.

Females with BD more commonly had arthritis and genital ulcers than males in our study and other previous results [8,12,31]. Interesting, although IBP is still uncertain as occurring as a clinical feature of BD, it presented in 33.7% of our patients, especially in female patients. So far several case reports have suggested the possible coexistence of BD and ankylosing spondylitis (AS) [32,33]. Our series did not include AS patients and IBP seemed to be associated with BD. Further studies will be required on the axial joint involvement in BD. Previous studies reported that vascular and ocular involvement was observed more frequently in males [10-11,17]. However, our study showed no differences in major organ involvements between genders, although uveitis was observed more frequently in males only at the onset of BD.

To evaluate the effect of age at disease onset on BD clinical features, we divided the patients into two groups based on the reference age of 40 that was suggested by a previous study [17]. This age could reflect the point when the levels of sex hormones changed abruptly. Some previous studies have reported the possible influence of sex hormones such as testosterone and androgen on BD [34,35]. In our study, neurologic involvement was more frequent in BD patients with late onset than those with early onset. From Turkish studies, it was reported that genital ulcers and ocular involvement were more frequent in patients with early onset (< 40 years) [17]. Male patients with younger onset (≤ 25 years) had more frequent major organ involvement with immunosuppressive use [18]. This different clinical features according to the age at onset might influenced by change of sex hormone such as testosterone and prolactin [34-36].

HLA-B51, known to be linked the risk of BD, may influence the clinical features in BD patients. Our BD patients with HLA-B51 showed earlier onset, more pseudofolliculitis and less gastrointestinal and neurologic involvements, which is comparable to previous reports. On the contrary, an earlier study on Korean 61 patients with BD showed that the patients with HLA-B51 suffered with more frequent uveitis and erythema nodosum and suggested HLA-B51 might be a genetic marker of the severe disease as related with uveitis and complete BD [22]. These contrasting results of the earlier Korean study may be caused by the diagnostic criteria of BD differed from us. The previous study used RCJ criteria and 16% of enrolled patients satisfied the criteria of complete BD. Thus the patients with full-blown BD could be enrolled much more in the previous study. Another study from Tunisian patients revealed that HLA-B51 was associated with a lower frequency of arterial aneurysm and neurological involvement although it was related with high frequency of eye involvement [23]. A meta-analysis of the relationship between HLA-B51/B5 and clinical manifestations in BD, HLA-B51/B5 was associated with moderately higher prevalence of eye involvement and lower prevalence of gastrointestinal involvement [21].

In conclusion, our study suggested that BD has the different clinical phenotypes according to gender, age at onset, and HLA-B51 status. Age at onset and HLA-B51 status may influence on the major organ involvements. Further investigation will be required on the influences of these factors on the clinical course and prognosis of BD patients.

#### KEY MESSAGE

1. Behcet disease (BD) has the different clinical phenotypes according to gender, age at onset and human leukocyte antigen (HLA)-B51 status.
2. In BD, age at onset HLA-B51 status may influence on the major organ involvements.

#### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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