

Influence of Sex on Patients with Behçet's Disease in Korea

Behçet's disease (BD) is a multisystemic inflammatory disorder known as having a histopathological findings of vasculitis. The influence of sexual difference on BD is a well-known fact and there are several reports suggesting a more severe course of the disease among young males. The purpose of our study was to determine the effects of gender on the severity and clinical features of BD patients in Korea. The study included 1,901 patients with BD who fulfilled the criteria of International Study Group for Behçet's Disease or corresponded to the complete or incomplete type for the revised criteria of Behçet's Disease Research Committee of Japan. BD in Korea showed a female predominance (M:F=0.61:1). The skin lesions were observed in 79.9% of patients, of which 77.6% had erythema nodosum-like lesion, which was more frequent in females. The ocular lesions were more common in males showing a higher frequency of uveitis. Ocular and vascular symptoms as clinical features with severe complications or mortality were more frequent in males than in females. The mean age at the onset of patients with the worst prognosis such as ocular, gastrointestinal, neurologic, and vascular involvements was significantly younger in male than in female patients ($p<0.05$). In conclusion, this study elucidated the influences of sexual difference on BD in Korea.

Key Words : Behçet Disease; Sex; Morbidity

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INTRODUCTION

Behçet's disease (BD) is a chronic and systemic disease that may involve multiple organs (1). It was first described in 1937 by the Turkish dermatologist Hulusi Behçet as a symptom complex of recurrent oral ulcers, genital ulcers, and uveitis (2). Several aspects of the immunopathogenesis are considered but its accurate etiology and pathogenesis are still unknown. Its clinical course is characterized by exacerbations and remissions of unpredictable duration and frequency.

The influence of sexual difference on BD is a well-known fact and there are several reports suggesting a more severe course of the disease among young males (1, 3). This aspect has never been studied in Korea. The purpose of our study was to determine the effects of gender on the severity and clinical features of BD patients in Korea.

MATERIALS AND METHODS

We carried out a retrospective review of the clinical records of 1,901 patients with BD who visited Behçet's Disease Speciality Clinic of Yonsei University College of Medicine and Ajou University School of Medicine from 1985 to 2000. The patients fulfilled the criteria of International Study Group

for Behçet's Disease (4) or corresponded to the complete or incomplete type for the revised criteria of Behçet's Disease Research Committee of Japan (5).

Medical records concerning epidemiological and clinical features of BD were made by dermatologists, saved as a computer database, and analyzed according to the sexual difference. The age at onset in BD patients was defined as the age with initial presentation of BD symptoms. Inflammatory arthritis with arthralgia, redness and swelling, as well as chronic, recurrent, asymmetrical arthralgia except for transient arthralgia and degenerative arthralgia were regarded as the articular involvements. Gastrointestinal ulceration confirmed by colonoscope was regarded as the gastrointestinal involvements. Statistical analyses were performed by chi-square test for a comparison between the gender and the clinical features of BD patients and by Student's t-test for a comparison between the gender and the mean age at onset. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Sex distribution

The male-to-female ratio was 0.61:1 showing the female

predominance. The male-to-female ratios in the complete and incomplete types of BD were 0.83:1 and 0.55:1, respectively.

Age distribution

The mean age of onset was 33.2 yr. The most common age of onset was in the 30s (39.0%), followed by the 20s (31.0%), the 40s (15.7%), and teens (7.9%). There was no statistically significant difference between males and females in the mean age at onset (Table 1).

Clinical features of major and minor symptoms

The frequencies of the major and minor clinical manifestations in 1,901 patients were as follows in decreasing order; oral ulcer (99.7%), genital ulcer (80.2%), skin lesion (79.9%), ocular lesion (51.2%), articular symptom (36.8%), gastrointestinal symptom (3.2%), vascular symptom (1.7%), and neurologic symptom (1.5%). Among those symptoms, ocular symptom ($p<0.0001$) and vascular symptom ($p<0.0001$) were more frequently observed in male patients, while oral ulcer ($p=0.022$), genital ulcer ($p<0.0001$), skin lesion ($p<0.0001$),

Table 1. Age and sex distribution at the disease onset

Age (yr)	Male	Female	Total	<i>p</i> -value
	Number (%)	Number (%)	Number (%)	
Under 10	6 (0.9)	15 (1.4)	21 (1.2)	
11-20	47 (7.0)	93 (8.5)	140 (7.9)	
21-30	231 (34.6)	317 (28.8)	548 (31.0)	
31-40	247 (37.0)	442 (40.2)	689 (39.0)	
41-50	101 (15.1)	176 (16.0)	277 (15.7)	
51-60	32 (4.8)	42 (3.8)	74 (4.2)	
Over 60	4 (0.6)	14 (1.3)	18 (1.0)	
Total	668 (100)	1,099 (100)	1,767 (100)	
Mean Age*	33.1±9.9	33.3±10.3	33.2±10.2	
M:F ratio	0.6	1	0.6:1	

*Values are mean ± SD.

Table 2. Clinical features of male and female patients with Behçet's disease

Symptoms	Male	Female	Total	<i>p</i> -value
	Number (%)	Number (%)	Number (%)	
Major				
Oral ulcer	717 (99.3)	1,178 (99.9)	1,895 (99.7)	0.022
Genital ulcer	537 (74.4)	987 (83.7)	1,524 (80.2)	<0.0001
Skin lesion	531 (73.5)	988 (83.8)	1,519 (79.9)	<0.0001
Eye lesion	466 (64.5)	508 (43.1)	974 (51.2)	<0.0001
Minor				
Articular	237 (32.8)	462 (39.2)	699 (36.8)	0.005
Gastrointestinal	21 (2.9)	39 (3.3)	60 (3.2)	ns
Vascular	24 (3.3)	8 (0.7)	32 (1.7)	<0.0001
Neurologic	3 (0.4)	25 (2.1)	28 (1.5)	0.003

ns: not significant.

articular symptom ($p=0.005$), and neurologic symptom ($p=0.003$) were more frequent in female patients (Table 2).

Cutaneous manifestations

Cutaneous involvement was seen in 79.9% of patients. The most frequent skin lesion was erythema nodosum-like lesion observed in 62.0% of patients; less frequent symptoms were folliculitis (4.2%), furuncle (4.2%), erythema multiforme (3.5%), ulcer (0.9%), abscess (0.8%), pustule (0.7%), acneiform eruption (0.4%), and thrombophlebitis (0.3%). Females had a higher frequency of erythema nodosum-like lesion ($p<0.0001$), whereas males presented more often with furuncle ($p=0.003$), erythema multiforme ($p=0.021$), and abscess ($p=0.022$) (Table 3).

Table 3. Analysis of skin lesions in patients with Behçet's disease according to sex

Skin lesions	Male	Female	Total	<i>p</i> -value
	Number (%)	Number (%)	Number (%)	
Erythema nodosum-like lesion	385 (53.3)	793 (67.3)	1,178 (62.0)	<0.0001
Folliculitis	26 (3.6)	53 (4.5)	79 (4.2)	ns
Furuncle	43 (5.9)	37 (3.1)	80 (4.2)	0.003
Erythema multiforme	34 (4.7)	32 (2.7)	66 (3.5)	0.021
Ulcer	7 (1.0)	11 (0.9)	18 (0.9)	ns
Abscess	10 (1.4)	5 (0.4)	15 (0.8)	0.022
Pustule	6 (0.8)	7 (0.6)	13 (0.7)	ns
Acneiform eruption	2 (0.3)	5 (0.4)	7 (0.4)	ns
Thrombophlebitis	4 (0.6)	2 (0.2)	6 (0.3)	ns
Others	29 (4.0)	59 (5.0)	88 (4.6)	ns

ns: not significant.

Table 4. Analysis of eye lesions in patients with Behçet's disease according to sex

Eye lesion	Male	Female	Total	<i>p</i> -value
	Number (%)	Number (%)	Number (%)	
Uveitis	241 (33.4)	179 (15.2)	420 (22.1)	<0.0001
Cataract	44 (6.1)	39 (3.3)	83 (4.4)	0.004
Retinal detachment	9 (1.3)	11 (0.9)	20 (1.1)	ns
Retinal hemorrhage	14 (1.9)	5 (0.4)	19 (1.0)	0.001
Glaucoma	11 (1.5)	8 (0.7)	19 (1.0)	ns
Retinal degeneration	1 (0.1)	4 (0.3)	5 (0.3)	ns
Others	158 (21.9)	252 (21.4)	410 (21.6)	ns

ns: not significant.

Table 5. Comparison between male and female patients with clinical manifestations of Behçet's disease which cause disability, mortality, or severe sequelae

Symptoms	Male (n=722)	Female (n=1,179)	Total (n=1,901)	p-value
	Number (%)	Number (%)	Number (%)	
Ocular*	316 (43.8)	254 (21.5)	570 (30.0)	<0.0001
Gastrointestinal	21 (2.9)	39 (3.3)	60 (3.2)	ns
Neurologic	3 (0.4)	25 (2.1)	28 (1.5)	0.003
Vascular	24 (3.3)	8 (0.7)	32 (1.7)	<0.0001

ns: not significant.

*Conjunctivitis and other specific ocular symptoms were excluded from severe clinical features of BD due to their poor correlation with BD. However, because cataract, retinal detachment, retinal hemorrhage, and glaucoma could occur as a complication of BD, these symptoms were included.

Ocular symptoms

Table 7. Age and sex distribution of Behçet's disease from selected reports*

Author	Origin	No. of patients	M:F	Age of onset (yr)	
				Mean	Range
Oshima	Japan	85	1.7:1	27	6-65
Chajek	Israel	41	4.9:1	27.4	15-54
Chajek	Various	683	2.3:1	25.9	6-72
Chamberlain	U.K.	32	0.6:1	24.7	10-61
O'Duffy	U.S.A.	10	0.4:1	35.2	16-67

*Cited from reference 11.

Ocular symptoms were found in 51.2% of patients. The most frequent ocular symptom was uveitis observed in 22.1% of patients; less frequent symptoms were cataract (4.4%), retinal detachment (1.1%), retinal hemorrhage (1.0%), glaucoma (1.0%), and retinal degeneration (0.3%). Males had higher frequencies of uveitis ($p<0.0001$), cataract ($p=0.004$), and retinal hemorrhage ($p=0.001$) (Table 4). Other ocular symptoms included chronic, recurrent conjunctivitis, scleritis, keratitis, optic neuritis, and retinal neovascularization.

The effects of gender on the severity and clinical features of BD patients

Conjunctivitis and other specific ocular symptoms were excluded from severe clinical features of BD due to their poor correlation with BD. However, because cataract, retinal detachment, retinal hemorrhage, and glaucoma could occur as a complication of BD, these symptoms were included. Also, gastrointestinal ulceration confirmed by colonoscope was regarded as a severe clinical feature of BD as it could cause perforation and hemorrhage followed by mortality. Ocular symptoms and vascular involvements as clinical features with severe complications or mortality were more frequent in males

Table 6. Age and sex distribution at the disease onset in patients with Behçet's disease with the worst prognosis such as ocular, gastrointestinal, neurologic, and vascular involvements

Age (yr)	Male	Female	Total
	Number (%)	Number (%)	Number (%)
Under 10	4 (1.2)	8 (2.7)	12 (1.9)
11-20	19 (5.7)	26 (8.7)	45 (7.1)
21-30	127 (38.3)	84 (28.2)	211 (33.4)
31-40	123 (37.0)	108 (36.2)	231 (36.6)
41-50	44 (13.3)	45 (15.1)	89 (14.3)
51-60	13 (3.9)	17 (5.7)	30 (4.8)
Over 60	2 (0.6)	10 (3.4)	12 (1.9)
Total	332 (100)	298 (100)	630 (100)
Mean Age*	32.6 ± 9.7 [†]	33.9 ± 12.2 [†]	33.2 ± 10.9

*Values are mean ± SD, [†] $p<0.05$.

Table 8. Comparison of clinical manifestations of BD between various parts of the world and this study (%)*

Symptoms	Japan ⁵ (n=3,316)	Germany ¹⁵ (n=141)	Turkey ¹⁶ (n=496)	Greece ¹⁷ (n=101)	This study (n=1,901)
	Oral ulcer	98	97	99.6	100
Genital ulcer	73	78	77	78	80.2
Skin lesions	87	75	78	75	79.9
Eye lesions	69	48	47	73	51.2
Articular	57	60	47	54	36.8
Neurologic	11	14	8	20	1.5
Vascular	9	25	38	11	1.7
Gastrointestinal	16	21	5	4	3.2

*Cited from reference 17.

than in females ($p<0.0001$ and $p<0.0001$, respectively) (Table 5). Neurologic involvements were more frequent in females than in males ($p=0.003$). Severe gastrointestinal involvement was not significantly different between males and females.

The effects of gender on the mean age at onset in BD patients with the worst prognosis

The mean age at onset in patients with the worst prognosis such as ocular, gastrointestinal, neurologic, and vascular involvements was significantly younger in male than in female patients ($p<0.05$) (Table 6).

DISCUSSION

The male-to-female ratio in BD patients in Korea was previously reported to be between 0.94:1 and 0.63:1 (6-10). In our study, the sex ratio was 0.61:1. The ratios have somewhat varied according to reports, however, female predominance was a consistent finding. This is similar to the reports from U.S.A. and European countries. However, most series from

other countries documented a male predominance (Table 7) (11, 12).

The age of onset has been most commonly reported in the 20s, ranging from 24.7 to 35.2 yr (1, 13, 14). In our study, the peak age of onset occurred in the 30s (39.0%) with a mean age of 33.1 yr in males and 33.3 yr in females. There was no statistically difference between males and females in the mean age at onset. However, the mean age at disease onset was younger in male BD patients with the worst prognosis such as ocular, gastrointestinal, neurologic, and vascular involvements than in female patients (32.6 ± 9.7 vs 33.9 ± 12.2 yr, respectively).

The clinical features of BD in our study were different from those in various other countries. In Table 8, clinical features of BD in various countries were compared with ours. Oral ulcer, genital ulcer, skin lesion, and eye lesion were found in a similar frequency, while articular, gastrointestinal, vascular, and neurologic involvements were found in a lower frequency in our study than others (Table 8) (5, 15-17).

Among the major criteria, skin lesions were observed in 79.9 % of patients, of which 77.6% had erythema nodosum-like lesion, which was more frequent in females as in the data reported from Turkey (3, 12). The ocular lesions were more common in males showing the higher frequencies of uveitis, cataract, and retinal hemorrhage. Among the minor criteria vascular involvement was more common in men and articular and neurologic involvements were more common in women. Gastrointestinal involvement was not significantly different between males and females. Several studies on the evaluation of the clinical findings according to sex have shown that the vascular and the neurologic involvements were significantly more frequent in males than in females (1, 3, 12, 18).

Risk factors for the degree of systemic involvement in BD have not yet been studied. We found a significant correlation between sex and several aspects of BD. Yazici et al. (3) also reported the male sex and younger age of disease onset (<25 yr) are associated with a more severe disease. Dilsen et al. (19) reported that male patients with earlier disease onset (<25 yr) had the higher prevalence of vital organ involvement. Moreover, Madanat et al. (12) reported that male patients with BD had a more severe course of the disease with higher frequencies of severe eye disease and neurologic involvement. The present study reveals that severe clinical features occurred more frequently in males at earlier ages than in women in Korea as in several reports. However, Demiroglu and Dundar (20) reported that younger patients with BD had a more severe course, but the clinical severity was not influenced by gender. Krause et al. (21) reported that there was no significant difference in the expression of BD between males and females and that patients with an older age at onset had systemic organ involvements more frequently.

In conclusion, this study might suggest some informations about the influences of sexual difference on BD in Korea. Further researches are anticipated on the factors related to the

sexual difference such as hormones or race.

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