



Epidemiologic and Etiological Features of Korean Patients With Behçet's Disease

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Behçet's disease (BD) is a multisystem disease in which environmental factors provoke an adverse immune response in patients with genetic susceptibility towards BD, subsequently leading to a cascade of dysregulated inflammation throughout the body. It is particularly prevalent in regions spanning the ancient Silk Road, including Korea, where the first known case of BD was reported in 1961. We summarize the history, epidemiology, and clinical presentation of BD in Korea, highlighting the clinical tendencies that are particularly seen in the Korean BD population as compared to European populations. Analysis of epidemiologic trends over the past three decades in Korea shows a decreasing prevalence of complete BD and a higher prevalence of intestinal BD. We also discuss the ever-evolving understanding of the pathogenesis of BD, noting the complex interplay among genetics, environment, and immunology. The HLA-B51 allele is the most significant known genetic risk factor in developing BD. We also discuss more recently studied associations between BD and immune factors such as IL-10, IL-23R-IL-12RB2, IL-1A-IL-1B, CCR1, ERAP1, and the GIMAP cluster, the last of which has been found to have an association with BD specifically in Korea. Environmental factors such as pollution and microbials are often the inciting event in developing BD, as they trigger an imbalanced immune response in genetically susceptible individuals, one that has been often found to exhibit an aberrant Th1/Th17 response. There would be value to further studying the pathogenesis and clinical characteristics of Korean BD. (*J Rheum Dis* 2021;28:183-191)

Key Words. Behçet syndrome, HLA-B51, Epidemiology, Genome-wide association studies

INTRODUCTION

Behçet's disease (BD) is a multisystemic, inflammatory disease with a chronic, relapsing course. It is characterized by a variety of clinical manifestations, including recurrent oral and genital ulcers, inflammatory skin lesions, and involvement of ocular, vascular, articular, gastrointestinal, and neurologic systems. The prevalence of BD is higher in regions of the ancient Silk Road, spanning from the Mediterranean to East Asia. Populations in this region exhibit a higher frequency of the HLA-B51 allele, which is the most important genetic susceptibility factor in the development of BD. Despite this common genetic component, there are significant differences in the clinical

characteristics of BD in the Mediterranean/Middle East versus East Asia, including Korea. In this review, we will discuss the history and clinical manifestations of BD in Korea, as well as the genetic and environmental factors that play a role in the pathogenesis of the disease.

HISTORICAL BACKGROUND

The earliest reports of BD in Korean literature were two cases described by the ophthalmologist Dr. Joo in 1961 [1]. A subsequent case report in 1962 described four cases of BD, one with severe systemic manifestations of the disease [2]. Anecdotal cases have continued to be reported in Korean literature from that point on.

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On November 10th, 1983, the Behçet’s Disease Specialty Clinic—the first of its kind in Korea—opened at the Severance Hospital of Yonsei University College of Medicine as a joint effort among the departments of Dermatology, Ophthalmology, and Otorhinolaryngology [3]. Korean researchers joined the international BD society and presented the first set of compiled domestic data at the 4th International Conference on BD in London on September 5~6th, 1985. Finally, on March 4th, 1999, a meeting was held regarding the organization of a Korean academic society for BD [4]. It was attended by 35 physicians. Professor Sungnack Lee was appointed as the first president of the Korean Study Group for BD (which was renamed as the Korean Society for BD [KSBD] later), and the first Annual Academic Meeting of KSBD was held on October 2nd, 1999, with presentations from lecturers Drs. Colin G. Barnes (UK) and Shigeaki Ohno (Japan) [4]. Finally, the 9th International Conference on BD was held on May 27th to 29th, 2000, in Seoul, Korea [5]. As of August 2021, KSBD (President, Prof. Eun-So Lee) has held 21 annual meetings.

DIAGNOSTIC CRITERIA FOR BD

At present, a final diagnosis of BD is made based on clinical presentation, as there are no laboratory markers of high diagnostic value. The International Study Group (ISG)’s diagnostic criteria for BD published in 1990 is the most widely recognized and used criteria [6]. It was further revised in 2014 as the International Criteria for BD (ICBD) to increase diagnostic sensitivity, refining criteria for vascular and central nervous system (CNS) involvement [7]. However, epidemiological data in Korea shows

a higher prevalence of gastrointestinal (GI) BD and relatively fewer patients with vascular and CNS symptoms [8,9]. The ISG criteria showed 58% sensitivity when used with Korean BD patients, a sharp decline from the 92% sensitivity in the ISG study sample [10]. In this context, the Japanese diagnostic criteria, which includes GI involvement as a diagnostic criteria, may be useful in the Korean clinical setting [11]. There have been efforts to establish a more precise diagnostic criteria for BD in Korea, prioritizing GI symptoms over vascular and CNS manifestations [12,13]. In short, physicians should understand the benefits and limitations of the available criteria for BD diagnosis, and their adaptation in clinical practice should be met with careful prioritization and consideration of each criteria’s respective characteristics (Table 1) [14].

CLINICAL MANIFESTATIONS

BD is a disease characterized by widespread, multi-system inflammation, and it manifests itself in various organ systems. Mucocutaneous manifestations are key markers of BD, and their recognition may allow for early diagnosis and intervention. Oral ulcers are nearly ubiquitous across all cases and classified into three types 1) minor, 2) major, and 3) herpetiform ulcers (Figure 1). Genital ulcers are similar to oral ulcers in appearance and course but tend to be less recurrent. Various cutaneous presentations occur in BD patients, and multiple concurrent skin lesion types are often observed in a single patient (Figure 2) [15]. Papulopustular lesions and erythema nodosum-like panniculitis are the classic cutaneous symptoms. Less common lesions, such as superficial thrombophlebitis, Sweet’s syndrome-like dermatosis,

Table 1. Comparison of diagnostic criteria for BD

Sign/symptom	ISG criteria (1990)	Japanese criteria (1987)	ICBD criteria (2014)
Oral aphthosis	□	◎	O (2 points)
Genital aphthosis	O	◎	O (2 points)
Skin lesions	O	◎	O (1 point)
Ocular lesions	O	◎	O (2 points)
Positive pathergy test	O	×	O (1 point)*
Joint involvements	×	O	×
Epididymitis	×	O	×
Intestinal involvement	×	O	×
Neurological manifestations	×	O	O (1 point)
Vascular manifestations	×	O	O (1 point)

□: required symptom, ◎: major symptom. BD: Behçet’s disease, ICBD: International Criteria for BD, ISG: International Study Group. *Optional in ICBD criteria. Adapted from the article of Kirino and Nakajima (Intern Med 2019;58:1199-207) [14].

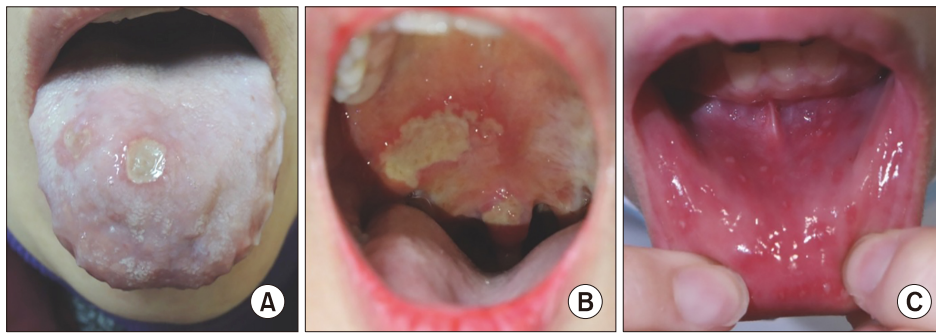


Figure 1. Clinical features of recurrent oral aphthous ulcers. (A) Minor ulcers, (B) major ulcers, (C) herpetiform ulcers. Ulcers ≤ 1 cm are considered minor ulcers while larger ulcers are considered major ulcers. Multiple scattered ulcers of several millimeters are considered herpetiform ulcers. Major ulcers may cause mucosal scarring and persist several weeks or longer.

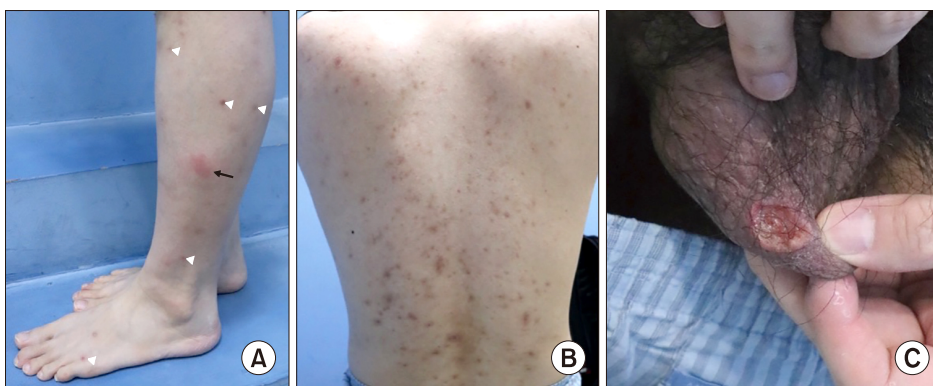


Figure 2. Cutaneous manifestations of Behçet's disease (BD). (A) Erythema nodosum-like lesion (arrow) and concurrent papulopustular lesions (white arrowheads) in lower leg. (B, C) Papulopustular lesion on trunk (B) and a scrotal ulcer in a male patient with BD.

pyoderma gangrenosum, and erythema multiforme-like lesions are also seen. Ocular manifestations of disease vary depending on site of involvement and include iridocyclitis, keratitis, episcleritis, scleritis, vitritis, and classic posterior uveitis, including retinal vasculitis and optic neuritis. Severe involvement of the posterior chamber is particularly related to visual morbidity. A nationwide analysis revealed that BD was an important clinical risk factor for blindness in Korean patients with non-anterior uveitis [16].

Articular, vascular, neurological, and intestinal involvement is less common but also lead to significant morbidity and mortality in patients with BD. Vascular BD lesions can involve both arteries and veins, but deep vein thrombosis of the lower extremities is the most common presentation [17]. One of the largest cohorts on neuro-BD in Korea showed brainstem manifestations (43.9%) to be the most common, followed by multifocal (32.7%) and spinal cord (12.2%) manifestations [18,19]. About 27% of patients in this analysis exhibited a progressive disease course, thus highlighting the necessity of careful long-term follow-up in BD patients with neurological

symptoms. Intestinal BD exhibits characteristic ulcers in the gastrointestinal tract, clinical assessment of which is guided by endoscopy. Endoscopic guidelines for intestinal BD diagnosis were recently established by an expert group of gastroenterologists in Korea [20]. The clinical course of intestinal BD during the first 5 years are variable, but the majority of Korean patients with intestinal BD exhibit remission or mild clinical activity at the 5 year mark [21]. Volcano-shaped ulcers, higher C-reactive protein levels, a history of postoperative steroid therapy, and the presence of intestinal perforations detected by pathology are poor prognostic factors in intestinal BD [22].

Recent studies suggest the overall severity of BD in Korea tends to be milder than BD at-large. Our chronological analysis of a large, single-center in Korea over the last three decades shows decreased prevalence of the major features of BD as well as an increased age of initial disease presentation [8]. The study additionally showed a clinical evolution of BD that is decreasingly of the symptomatically complete type, being characterized by less ocular involvement and increased intestinal involvement. Similarly, analysis of BD patients' ophthalmology clinic

visits over the past two decades revealed that recent BD patients experience significant less ocular involvement and a better visual prognosis [23]. This clinical pattern of decreasing complete-type BD and increasing GI-type BD was similarly identified in Japanese patients [24]. This may be due to improved hygiene practices preventing adverse microbial-immune interactions, greater public awareness of BD, and improved healthcare resources.

EPIDEMIOLOGY OF BD IN KOREA

Three epidemiological studies using the national health database gave recent reports regarding the estimated prevalence of BD in Korea. The Health Insurance Review & Assessment (HIRA) data from 2011~2015 reported an estimated prevalence of Korean BD of 32.8~35.7 per 100,000 population [25]. Analysis from the Korean National Health Insurance Service Claims Database from 2006 to 2015 reported the mean prevalence of BD in Korea to be 26.195 patients per 100,000 population [26].

Given these estimated prevalence reports and the total population of Korea (51.71 million in 2019), there can be estimated to be 13,500 to 18,500 registered BD cases nationwide. Despite this rough estimate, the prevalence of BD in Korea is not fully known, as reflected in the discrepancies amongst various nationwide dataset analyses. Based on the increasing trend of registered BD patients in the HIRA dataset, Kim et al. [25] anticipates a higher prevalence of BD, 36.9 (95% confidence interval [CI] 35.0~39.0) to 44.7 (95% CI 40.2~49.6), between the years 2016 and 2025. Conversely, Lee et al. [26] reported the incidence of BD in Korea to have decreased from 7.474 cases in 2006 to less than 2.6 cases per 100,000 population in 2015. Similarly, Jun et al. [27] reported that the annual incidence of BD had decreased from 8.15 to 1.51 per 100,000 population based on the HIRA dataset from 2004 to 2017. Prevalence reports should thus be cautiously interpreted, given the multiple conclusions of various analyses.

PATHOGENESIS

The exact pathogenesis of BD remains largely elusive. However, it is generally accepted that the initial BD presentation is incited by environmental factors, such as infectious agents of pollution, acting on patients of genetic susceptibility [28]. With this background in mind, this review will briefly summarize the complex etiology of BD

in two parts, 1) genetic factors and 2) environmental factors and immunopathogenesis. It will do so while highlighting recent updates on the Korean BD patient population.

Genetics

Human leukocyte antigen (HLA)-B51 is believed to be the strongest risk factor for BD. Meta-analysis on HLA-B51/B5 in BD from 78 independent studies revealed that HLA-B51/B5 allele carriers have an increased risk of developing BD compared to non-carriers with a pooled odds ratio (OR) of 5.78 (95% CI 5.00~6.67) [29]. Subgroup analysis of BD throughout East Asia showed OR 5.18 (4.15~6.47), suggesting HLA-B51 as a consistent risk factor for development of BD across various ethnicities. This analysis fails to isolate HLA-B51 from the HLA-B5, HLA-B52 split antigen, the latter of which is not related to BD susceptibility, and thus likely represents a small underestimation of the true genetic contribution of HLA-B51 in the development of BD. A strong gene interaction was recently found between HLA-B51 and ERAP1, a gene encoding for an aminopeptidase that is primarily responsible for final peptide trimming in the endoplasmic reticulum. HLA-B51 is therefore considered a key mediator of the aberrant inflammation in the 'MHC-I-opathy' of BD [30,31].

The reported prevalence of HLA-B51 in Korean patients with BD varies depending on inclusion criteria or the specialties of enrolling institutes. Overall, 40.8%~55.7% of BD shows HLA-B51 positivity in Korea [32,33]. Similarly, a recent analysis on Japanese BD registered in the Ministry of Health, Labour and Welfare of Japan showed 44.5% of BD patients, diagnosed based on the ICBP criteria, were HLA-B51-positive [34]. In this study, HLA-B51-positive patients in Japan had a higher risk for ocular lesions (OR 1.59, 95% CI: 1.37~1.84) and a lower risk for genital ulcers (OR 0.72, 95% CI: 0.62~0.84; $p < 0.001$) and GI symptoms (OR 0.65, 95% CI: 0.55~0.77). Of note, HLA-B51 positivity has been found to have a much stronger association with non-intestinal-type BD than intestinal BD in both Korean and Japanese patients [35], suggesting that intestinal BD may have a distinctive immune-genetic profile, particularly in Far East Asia [36].

To date, many genome-wide association studies (GWAS) have suggested IL-10, IL-23R-IL-12RB2, IL-1A-IL-1B, CCR1, and ERAP1 as additional susceptibility genes for BD [30,37,38]. Independent GWAS and linkage analysis

reproduced the association of BD and IL-23R-IL-12RB2 in the Korean population but not between BD and IL-10 or ERAP1 [39,40]. Notably, the GIMAP cluster, which is involved in T-cell survival, was identified as a novel susceptibility loci for Korean BD, thus suggesting that aberration of the T-cell response may contribute to the development of Korean BD. This association between the GIMAP cluster and BD has not been replicated in European populations [41], suggesting that varying genetic predispositions of geographically-different populations may induce different immunopathogenic profiles of BD. Interestingly, single nucleotide polymorphisms in IL17A had a positive association with the development of intestinal BD in the Korean population, suggesting a close relationship between genetically predisposing factors and ethnicity-specific disease features [42]. HLA-A*26 has also been identified as an independent-risk HLA allele in Korean BD [43]. It has also been determined to be

a relatively high-risk allele in the Japanese population, specifically within the HLA-B*51-negative population (OR 4.02, 95% CI: 2.29~7.05) [44]. Given this finding, the role of HLA-A in the immunopathogenesis of Korean BD should be further studied and elucidated. Studies on genetic predisposition of BD in Korean population is summarized in Table 2 [39,40,42,43,45-49].

Environmental factors and immune response

The environmental factors triggering BD development include microorganisms and environmental pollutants [28]. Among infectious agents, common bacteria such as *Streptococcus sanguinis* and viruses such as herpes simplex virus (HSV) have been widely investigated. As improved oral hygiene practices are correlated with an improved disease course [50], it is evident that oral commensals have a direct or indirect role in the pathogenesis of BD. Notably, streptococcal 65-kDa heat shock protein

Table 2. Summary of studies on genetic predisposition of BD in Korean population

Author	Year	Method	Patient number	Outcome
Kwon et al. [45]	2019	Genotyping for 20 targeted mitochondrial SNPs	98 BD patients 196 controls	m.16812A>C and m.16183A>C are more frequently observed in BD patients than controls
Kang et al. [39]	2017	Genotyping for SNPs in IL23R-IL12RB2, IL10, STAT4, and ERAP1	369 BD patients 2000 controls	IL23R-IL12RB2 intergenic SNPs rs1495965, rs1495966, rs4655535 significantly associated with BD risk
Kang et al. [40]	2014	Genotyping of 24 SNPs in JAK1, STAT3, and TYK2	223 BD patients 222 controls	No association with SNPs in IL-10 mediated signaling pathways (JAK1, TYK2, STAT3)
Lee et al. [46]	2013	GWAS using Affymetrix genome-wide human SNP array 6.0	379 BD patients 800 controls	Association of BD to GIMAP locus on chromosome 7q36, as well as an association with four SNPs: rs1522596 in GIMAP4, rs10266069 and rs10256482 in GIMAP2, and rs2286900 in GIMAP1
Kim et al. [42]	2012	Genotyping for SNPs in IL17A, IL23R, and STAT4		TT genotype of IL17A rs8193036 and GG+GT genotype of IL23R rs1884444 associated with development of intestinal BD
Kang et al. [43]	2011	Genotyping for HLA-A locus	223 BD patients 1,398 controls	HLA-A*02:07, A*26:01, and A*30:04 increased risk for BD; HLA-A*33:03 decreased risk for BD
Park et al. [47]	2009	Investigation of polymorphisms of promoter region and exon 1 of CTLA4 gene	285 BD patients 287 controls	CTLA4-1661 GG and CTLA4-1722 TC genotypes significantly higher in BD patients than controls. CTLA4-1722 CC genotype significantly lower in BD patients with ocular symptoms
Kim et al. [48]	2006	Analysis of three polymorphisms in SLC11A gene (5'promoter (GT)n, D543N, A318V)	99 BD patients 98 controls	Allele 3 and genotype allele3/allele 3 of 5'-promoter (GT)n in SLC11A1 gene had significantly lower risk of developing BD than control
Park et al. [49]	2002	Investigation of MICA polymorphism in relation to HLA-B51 positivity and BD clinical manifestations	108 BD patients 204 controls	MICA*A6, rather than HLA-B51 positivity, is more strongly associated with Korean BD patients

BD: Behçet's disease.

(HSP) from oral *S. sanguinis* has been reported to be an important trigger in the pathogenesis of BD [51]. Our group demonstrated that the *S. sanguinis* HSP, GroEL protein, is the target of a serum anti-endothelial IgA antibody, suggesting that molecular mimicry between bacterial and host proteins may activate autoreactive lymphocytes and lead to autoantibody production in the development of BD [52].

Studies have identified HSV-1 in the active mucosal lesions of patients with BD via polymerase chain reaction [53,54]. Inoculation of HSV-1 (KOS strain) in the ears of ICR mice successfully induced a BD-like animal model, which is now the most widely-tried mouse model in translational studies [55,56]. Notably, HSV-inoculated mice showed higher incidence of BD-related symptoms under conventional conditions than those under specific pathogen free conditions (15.0% vs. 2.2%), suggesting that environmental stressors and a subsequently altered microbiome play pivotal roles in provoking the pathogenic inflammation induced by the anti-HSV immune response seen in BD [57]. Environmental pollutants are thought to be significant contributors in the development of BD [28,58]. This is with the exception of smoking nicotine which, based on recent epidemiological analysis using a nationwide database, may be a potential protective factor [59].

Pathogenic BD phenotypes are the consequence of an aberrant immune response induced by both genetic predisposition and environmental factors. Immune responses are largely classified into innate and adaptive responses.

A few BD-risk alleles found in the Korean population, such as KLRC4 [30] and MICA [49], support the role of natural killer (NK) cells in the development of BD [60]. NK cells, innate cytotoxic cells, regulate the function of other immune cells, including dendritic cells and T-cells. KLRC4 may act as a receptor for the identification of MHC class I molecules. Although the exact role of NK cells in BD remain unclear, an alteration in a subset of NK cells may lead to the imbalance in the Th1 response and immunoregulatory role of NK cells [61].

BD patients exhibit high intrinsic activation of neutrophils, which are involved in the vasculitic infiltration of BD lesions. High levels of proinflammatory cytokines and chemokines, such as IL-8, tumor necrosis factor- α , interferons, granulocyte macrophage colony-stimulating factor (GM-CSF)/G-CSF, and CXCL-8 are closely related with the activation of neutrophils in BD [60].

Increased chemotaxis, phagocytosis and production of reactive oxygen species from hyperactivated neutrophils may cause endothelial dysfunction and the subsequent vasculitis seen in BD [62]. Neutrophil extracellular traps also promote thrombosis by activating macrophages [63]. Skewed macrophage differentiation favoring the M1 type was also reported in BD lesions and experimental animal models [64,65].

Overproduction of inflammatory cytokines by innate immune cells causes a hyperactive Th1- and Th17-mediated immune response in BD. As discussed in the section on genetic pathogenesis, IL23R dysregulation is associated with BD development. The disease-protective variant, IL23R R381Q, has been found to be associated with reduced IL-23-dependent IL-17 production [66]. Additionally, peripheral blood monocytes in BD patients tend to facilitate T-cell differentiation into Th1 and Th17 [67]. Thus, both genetic predisposition and the corresponding innate immune response are responsible for the Th1/Th17-skew in the T-cell activity seen in BD.

In short, environmental factors may trigger an innate immune reaction in patients with BD that exhibits an aberrant Th1/Th17 response, subsequently leading to inflammation and disease progression.

CONCLUSION

The pathogenesis and clinical presentations of BD in Korea is an ever-evolving area of understanding. Careful attention to the multifactorial genetic, immunologic, and environmental factors at play allows clinicians to make more precise BD management and screening recommendations, as well as informs future areas of study. Analysis reports on nationwide health datasets have been variable in regard to BD prevalence trends, and there would be value in systematically collecting and analyzing trends of BD in Korea over time. Further studies identifying risk factors and pathogenetic mechanisms specific to Korean BD would help refine management in the large number of BD patients in Korea.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

D.Y.K. conceived and planned the outline of review.
S.H.C. and D.Y.K. reviewed literatures and wrote the manuscript.

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