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Update on the epidemiology, risk factors and disease outcomes of Behçet's disease

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A B S T R A C T

Behçet's disease (BD) may be regarded as a polygenic autoinflammatory disease although adaptive immune system has also been implicated in pathogenesis. Different classification criteria sets exist for BD, including the new "International Criteria for BD." The pooled prevalence of BD was calculated as 10.3 per 100,000 population globally. BD is common along the Silk Road, including Turkey. Male sex and early onset are associated with a more severe disease course. For the follow-up of BD, there are five disease activity scales, one disease severity scale, and one QOL scale.

Introduction

Behçet's disease (BD) was first described as a trisymptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis [1] and later recognized as a multisystem inflammatory disease characterized by variable clinical manifestations, including the involvement of mucocutaneous, ocular, cardiovascular, musculoskeletal, gastrointestinal, central nervous, and pulmonary systems [2]. Its manifestations range from self-limiting symptoms, which may recur at varying intervals over many years, to severe clinical episodes that may lead to organ damage and even loss of life. BD can be described as a complex and multifactorial disease involving interactions of several genes with unclear environmental exposures. There is evidence for the implication of both adaptive and innate immune systems in the disease process [3]; however, the exact etiology and pathogenesis of BD remain unknown. BD shares some clinical and pathophysiologic features with autoinflammatory diseases, which include a relapsing remitting disease course, increased neutrophilic activity, elevated levels of IL-1β,

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enhanced inflammatory response, overexpression of inflammatory cytokines, and the lack of specific autoantibodies [4]. Therefore, it has been classified as a polygenic (complex genetic trait) or multifactorial autoinflammatory disease by some. The adaptive immune system is also implicated in the pathogenesis of BD, as indicated by strong association with HLA-B*51, symptomatic improvement with T-cell-suppressing therapies and existing evidence (though weak) for the involvement of HLA-B*51 cytotoxic $CD8^+$ T cells in BD lesions and ulcers [4]. Because of the involvement of both innate and adaptive immune responses in the disease process, BD has recently been proposed to be classified as a major histocompatibility complex (MHC)-I-opathy alongside with spondyloarthritis also known to be strongly associated with specific human leukocyte antigen (HLA) risk alleles. The MHC-I-opathy concept hypothesizes that the localized activation of innate immune cells at sites of barrier dysfunction and/or stress (mechanical or otherwise) triggers secondary $CD8^+$ T-cell responses with prominent neutrophilic inflammation [5].

This review primarily covers the recent research on the descriptive epidemiology of BD, as well as the risk factors, outcomes, and outcome measures of the disease.

Disease definition/classification

There is no specific biomarker or pathognomonic histologic feature for the diagnosis of BD. Therefore, its diagnosis relies mainly on clinical judgment based on a constellation of typical clinical features. To date, more than 15 classification criteria have been proposed for BD [6]. Since the development of the International Study Group (ISG) Criteria set (Table 1) in 1990, it has been the most frequently used criteria set in epidemiologic studies, because of its high sensitivity and specificity of 92% and 97%, respectively [7,8]. Fulfillment of the ISG criteria requires the presence of oral ulceration plus any two of the following items in the absence of other clinical explanations: genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test [7]. The ISG criteria have been used in more than half of the published prevalence studies of BD. The use of different classification criteria sets may potentially create a considerable heterogeneity between the studies, but this seems to have shown only a negligible effect on the variation in the reported prevalence estimates of BD [9]. This may be explained by the similar item content of the different classification criteria sets, relying on oral and genital ulcers and ophthalmological manifestations as main characteristics [10].

In 2014, a new initiative was launched to develop a new set of “International Criteria for Behçet's disease” (ICBD) because of the low sensitivity of the ISG criteria observed in some studies. The new criteria set was expected to be capable of “performing with good discriminatory potential regardless of country” and be “intuitive and easy to use in a wide variety of settings” [11]. The newly proposed criteria set did not use recurrent oral ulceration as an entry criterion but included vascular and

Table 1
International Study Group criteria for the diagnosis of Behçet's disease, adopted from Ref. [7].

Recurrent oral ulceration			
Minor/major aphthous or herpetiform ulceration	Observed by the physician or patient	At least three times in a 12-month period	
Plus any two of the following			
Recurrent genital ulceration	Eye lesions	Skin lesions	Positive pathergy reaction
• Aphthous ulceration or scarring observed by the physician or patient	• Anterior uveitis • Posterior uveitis • Cells in the vitreous by slit-lamp examination • Retinal vasculitis observed by an ophthalmologist	• Erythema nodosum observed by the physician or patient • Pseudofolliculitis • Papulopustular lesions • Acneiform nodules observed by the physician in postadolescent patients not on corticosteroids	• Read by the physician at 24–48 h

Findings applicable only in the absence of other clinical explanations.

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neurological features as new items and laid more emphasis on the presence of oral or genital ulcers and eye disease. In the original development cohort, the ICBD criteria exhibited a higher sensitivity than the older widely accepted ISG criteria, while maintaining comparably high specificity [11]. However, a very recent study that assessed the performance of the ICBD criteria set on an unselected British cohort reported that it had a very low specificity at 19%, considerably lower than the specificity of the ISG criteria of 69%, though it was also lower than expected [12]. These results advise caution for the use of the ICBD criteria as a tool for "mass screening and identification of possible BD by non-experts," as was originally intended [11]. Recently, a pediatric group has also suggested a classification criteria based on a childhood registry [13].

Disease occurrence

Prevalence

Epidemiologic studies conducted in many countries worldwide have reported highly variable prevalence estimates for BD, ranging from 0.1 per 100,000 population in Hawaii [14] to 664 per 100,000 population in Northern Jordan [15]. A recent systematic literature review and meta-analysis aimed to assess the effect of geographical, methodological and other study characteristics on the variation between the prevalence estimates of different studies [9]. The pooled prevalence of BD (expressed as cases per 100,000 population) was calculated as 10.3 (95% CI, 6.1–17.7) per 100,000 population globally, 119.8 (95% CI, 59.8–239.9) for Turkey, 31.8 (95% CI, 12.9–78.4) for the Middle East, 4.5 (95% CI, 2.2–9.4) for Asia, 5.3 (95% CI, 3.4–8.2) for Southern Europe, 2.1 (95% CI, 1.1–4.0) for Northern Europe, and 3.8 (95% CI, 2.2–6.8) for North America/Caribbean Islands. The authors of the meta-analysis concluded that geographic location and the type of the study design both had a considerable effect on the reported prevalence estimates of BD. The pooled prevalence for the studies using sample surveys (also known as field or population surveys) was found to be 22-times higher than that for the studies using census surveys (widely known as hospital-based studies). The results of this analysis also demonstrated that the classification criteria used for case definition, study period, type of source publication (peer-reviewed journal or gray literature) had only a trivial effect on the variability of the prevalence estimates. Although all the eligible studies included in the meta-analysis were required to report estimates referring to adult populations, the lower age limit for the definition of adult population differed across the studies, which could also contribute to the variability in the reported prevalence estimates for BD, though not addressed in this meta-analysis.

After this meta-analytical study, five new studies were published on the prevalence of BD, two from Korea [16,17], one from Turkey [18], one from Jordan [15], and one from Poland [19]. The two Korean studies estimated the prevalence of BD for the entire population as 35.7 per 100,000 and 26.7 per 100,000 [16,17]. These prevalence figures were 5- to 7-folds higher than the previously reported pooled estimate for Asia [9]. The study from Turkey used a two-staged, cross-sectional population-based design [18]. In the first stage of the study, randomly selected adults (aged $\geq$20 years) from 52 urban and 33 rural family physician practices were invited to family physician units where they were examined by three dermatologists. In the second stage, subjects with suggestive findings of BD were invited to the regional university hospital for pathergy testing, eye examination, and blood tests. This study calculated a very high prevalence of 600 (95% CI, 290–920) per 100,000 in the sample population. One major flaw of the method of the study was that the prevalence was calculated from the number of individuals who attended their scheduled appointments at the family physician units as the denominator population. Such an approach disregards the fact that subjects with a previous diagnosis of BD or with potentially related symptoms are very likely to be overrepresented among the attendees compared with the non-attendees. The Jordanian study, which also had a two-stage cross-sectional population based design [15], calculated a prevalence of 662 (95% CI, 348–975) per 100,000 in the study population, the highest ever reported worldwide. The first prevalence and incidence estimates of BD from Eastern Europe were only recently reported by a Polish study using a hospital-based design [19]. The prevalence of BD calculated in this study was 0.34 per 100,000, the second lowest prevalence observed in Europe after Scotland [20]. However, this figure is almost certainly an underestimate considering that the case finding strategy of the study would miss a portion of the patients.

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Incidence

Reliable and stable incidence rates of rare diseases can be estimated only by screening of large populations over prolonged periods of time. Therefore, the incidence of BD has been much less studied than its prevalence. In the few studies conducted in different countries, the incidence of BD per 100,000 has been estimated to be 3.97 in Korea [17], 0.75 in Japan [21], 1.0 in Germany [22], 0.66 in Spain [23], 0.65 in Western Switzerland [24], 0.24 in Italy [25], 0.20 in Sweden [26], 0.05 in Poland [19], and 0.38 in the USA [27], 0.72 in Martinique, France (populated by an African descent population) [28]. The notably higher incidence estimate in the Korean population is not unexpected, considering that Korea is one of the endemic areas for BD [19]. The incidence in Germany, the highest estimate in western populations, was based on the data from the national registry for BD, in which 45.3% of the patients were of Turkish origin [22]. Very low incidence figure found in the Polish study can be explained by the study design that identified only hospitalized patients [19].

Risk factors

Age and sex

Because the initial studies have suggested that male sex and a younger age of disease onset are risk factors for a more severe disease course in BD [29], demographic characteristics have been a major area of interest when studying the epidemiology of BD. The disease usually begins in the second decade of life, irrespective of the country of origin or gender [10,30]. The average age of disease onset was observed to be 26.7 years in men and 28.4 years in women in the German registry of BD [31]. An onset before the age of 15 years or after the age of 50–55 years has been suggested to be quite rare [10]. In the Korean nationwide epidemiologic study of BD, less than 3% of all the identified incident cases were elderly patients (≥70 years) [17]. The proportion of juvenile onset cases in several cohorts of BD was estimated to be in the range of 2–5% [32].

Gender predilection for BD has been a controversial issue in the epidemiology of BD. Male predominance reported in early studies from Japan and Turkey [29,33] has not been consistently confirmed by the following studies, some of which showed fairly balanced male-female distribution even in populations from the same countries [34–37]. A recent review article presented data from 33 countries regarding the male to female ratio (M/F) of BD. Male predominance (M/F > 1.1) was noted in 19 of these countries, whereas equal distribution was observed in 6 countries (M/F: 0.9–1.1) and female predominance (M/F: <0.9) in 7 countries [38]. Importantly, the type of patient recruitment strategy and the specialty of the study center may contribute to the variations in the gender ratios across the studies, because several lines of evidence suggest that there is a difference in clinical manifestations and disease severity between male and female patients with BD [29,39–43]. A comprehensive meta-analysis of 53 observational studies [31] confirmed the results of earlier studies suggesting that men had a higher risk of ocular [41–44] and vascular manifestations [41,43,44]. Moreover, folliculitis, papulopustular skin lesions, and a positive pathergy test were more frequent in men, whereas genital ulcers, erythema nodosum, and joint involvement were more frequent in women.

Genetics

Higher prevalence in specific geographic areas and ethnic populations, familial aggregation, high sibling recurrence rate, and strong association with HLA- B*51 suggest that genetic factors play a pivotal role in susceptibility to BD.

Studies from different countries have demonstrated variable rates of familial occurrence of BD. More frequent familial aggregation has been observed in families of Turkish (18.2%), Korean (15.4%), and Israeli origin (13.2%) than in families of Chinese (2.6%), Japanese (2.2%), and European origin (0–4.5%) [30,45,46]. The frequency of familial cases is significantly higher among pediatric patients (12.3%) than that among adult patients (2.2%) [47]. Inheritance from parents to off-spring is possible, but the recurrence risk in siblings is greater. In a Turkish population, a sibling recurrence rate of 4.2% was calculated [48]. It has been noted that HLA-B*51 prevalence among familial cases is considerably higher than that among sporadic cases [45]. In the only twin study reported to date, pairwise

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concordance rate was 33.3% (2/6) for monozygotic twins and 12.5% (1/8) for dizygotic twins [49]. From these values, the heritability of BD was estimated as 41%.

It has long been known that BD is associated with HLA−B*5/B*51 [50,51]. This association has been confirmed virtually in every population studied. A meta-analysis of 78 case-control studies computed a pooled odds ratio of 5.78 (95% CI, 5.00−6.67) for susceptibility to BD in HLA−B*5/B*51 allele carriers [52]. Although, HLA-B*5/B*51 had a variable pooled prevalence estimate across the regions defined in the study (ranging from 11% to 22% among controls and from 34% to 65% among patients), it exerted an even impact on disease susceptibility in all ethnic groups, with population-attributable risk estimates for different populations ranging from 32% to 52%. HLA-B*5/B*51 has a modest effect on disease phenotype [53]. Recent genome-wide association studies, except one, demonstrated that HLA Class I region had the strongest association with BD [54]. Further analysis of one of the studies indicated that among the genotyped polymorphisms in the region, HLA-B*51 showed the highest association [55]. However, HLA-B*51 alone is neither necessary nor sufficient for the development of BD and its role in susceptibility to BD remains an enigma.

Environmental factors

Environmental factors contributing to BD are much less studied than genetic factors. Similar to other multifactorial complex diseases, infectious agents have long been suspected to trigger the exaggerated inflammatory response for BD. Because of the increased incidence of tonsillitis and poor oral health in patients with BD, the role of streptococci, particularly of *Streptococcus sanguinis*, has been extensively investigated in the pathogenesis of the disease [56]. The microbiome of the oral cavity has been recently studied in patients from the UK [57] and Turkey [58]. The study from the UK found higher colonization of *Streptococcus* species at ulcer sites than in healthy controls and patients with recurrent aphthous stomatitis. A different microbiome profile was found in the saliva of Turkish patients [58] and in the gut of Italian patients in another study [59]. Both studies indicated significant reductions in bacterial species diversity, with distinct alterations in their microbiota composition compared to that in healthy controls [58,59]. However, thus far, no specific microorganism has been proven to be a causative agent for BD. A retrospective study found no deleterious effect of smoking on the clinical findings and prognosis of uveitis in patients with BD [60]. A recent meta-analysis of four prospective case control studies showed no association between vitamin D deficiency and BD [61].

Spatial and temporal variations in disease risk

Epidemiologic studies including immigrant and European populations noted higher prevalence estimates of BD among people of Turkish origin in West Berlin [62], among people of North African or Asian origin in Paris [63], among people of Turkish or Moroccan origin in Rotterdam, and among people of foreign ancestry, mostly of Middle Eastern origin in southern Sweden as compared to the native local people residing in the corresponding areas [26]. Differences in prevalence by ethnicity were also observed in a study conducted among Druze, Arabs, and Jews [64] and, to a lesser extent, in Kuwait between Arab and non-Arab populations [65]. The age of immigration does not seem to influence the prevalence of BD [63]. These results suggest that genetic rather than environmental influences explain the variation in disease occurrence.

However, a systematic review that assessed the data from four population-based studies, and seven non-population-based comparative studies found no evidence for disparate clinical expressions in populations from different geographic locations [66]. Therefore, properly designed studies using standardized criteria and clear ethnic definitions are needed to clarify this issue.

Two nationwide surveys in Japan revealed a small decrease in the incidence of BD from 0.89 per 100,000 in 1984 to 0.75 per 100,000 in 1990 [21]. Furthermore, several studies from well-established uveitis clinics in Japan indicated a temporal decrease in disease severity and in the prevalence of BD in newly diagnosed patients with uveitis [67–69]. A change in clinical expression toward a milder disease has also been observed in Korea, with fewer cases of full-blown disease, in recent years [70]. Notably, the incidence of BD in Korea decreased from 7.5 per 100,000 in 2006 to 2.5 per 100,000 in 2015 [17]. The downward temporal trend observed in the incidence and clinical severity of BD in Japan and Korea, both of which have fairly homogenous populations, can be explained by improvements in (oral or general) hygiene and socioeconomic conditions over time [71].

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Outcomes and outcome measures

Long-term outcomes

BD typically has a waxing and waning disease course. Disease activity is most intense in the early years and usually vanishes with time. A cross-sectional postal survey in the UK demonstrated that adult patients with long-lasting BD have a poorer health-related quality of life (HRQoL) than the general adult population and groups with other chronic conditions in the UK [72]. A follow-up study on the same cohort performed 4 years later using the same design showed that symptoms continued to have a negative impact on the patients' HRQoL, with arthropathy, headache, other neurological problems, pathergy reaction, and skin problems exerting the greatest effect [73]. Impairment of quality of life (QoL) in patients with BD was found to be correlated with the overall disease activity in a recent study [74] and with disease severity in an earlier study [75]. Mucosal, central nervous system, musculoskeletal, and ocular manifestations were the main factors that negatively affected QoL in the most recent study [74], whereas in the previous study, ocular and vascular involvement seemed to contribute to the impaired QoL [75].

Ocular, neurologic, and vascular involvement are recognized as the major causes of morbidity and mortality in patients with BD. Males are more often and more severely affected by these organ manifestations. Ocular disease and visual complications occur usually within the first few years of disease onset. Eye involvement developed within 5 years of diagnosis in more than 80% of patients of either sex [39]. Loss of useful vision was reported to be 17% at 5 years, 25% at 10 years, and 29% at 20 years [76]. Conversely, central nervous system and major vessel involvement may appear late in the disease course, 5–10 years after disease onset. Large vessel disease and parenchymal central nervous system disease are major causes of mortality [39]. Nonexistence of major organ involvement in the early stages of the disease does not necessarily connote a favorable prognosis, particularly in young male patients, because serious organ complications can appear later in the disease course [77,78].

A long-term retrospective follow-up study involving 387 Turkish patients reported an overall mortality rate of 10% over 20 years of follow-up [39]. Higher standardized mortality ratios were observed particularly among young males, especially for the 14- to 24-year age group, who demonstrated 10 times greater mortality than the background population. Later, a French study reported an overall mortality rate of 5% after a median follow-up of 7.7 years [40]. Similar to the Turkish study, the mortality rate was higher among younger patients and particularly among males [40]. Recently, the same group published 15-year mortality rates for patients with BD in three different multi-ethnic groups: 19% in patients of sub-Saharan African origin, 9% in patients of North African origin, and 6% of European origins [79]. Male gender, cardiovascular involvement, and sub-Saharan African origin were independently associated with mortality.

Outcome measures

The outcome measures that have been used in clinical trials of BD was the subject of a recent systemic literature review by The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group [80]. A considerable diversity and variability were noted in the outcomes and outcome measures used in the published trials [80]. Moreover, most of the measures used in the studies were not properly validated, and outcome variables such as response, relapse, or remission lacked standardized definitions.

As discussed in the systematic review, there are five disease activity scales (Behçet's Disease Current Activity Form (BDCAF), Clinical Disease Activity Index, Clinical Manifestations Index, Iranian BD Dynamic Activity Measure, and 1994 Criteria for Disease Activity of BD). In addition, there is one disease severity scale (Krause's total severity score) and one QOL scale (BD Quality of Life) that were developed for BS. There is also an organ-specific outcome measure "oral ulcer composite index" that was developed and validated for mucocutaneous BD. However, these outcome measures, though developed specifically for BD, were not widely used in studies of BD [80]. BDCAF, which is the most frequently used disease activity measure, has been used in only 10% of the studies. Krause's total severity score, the most commonly used index to evaluate disease severity, was used only in 6% of the published studies. Internet-based surveys performed by the OMERACT Vasculitis Working Group among expert physicians from relevant specialties from multiple countries highlighted the need for widely acceptable and properly validated outcome measures for BD [81]. To this end, qualitative interviews were

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conducted with patients to understand their perspective, and a Delphi exercise was conducted with both patients and physicians under the leadership of the OMERACT Vasculitis Working Group, who then selected a number of domains and subdomains to be measured in trials of BD. All the selected items received ≥70% endorsement by expert physicians and/or the patients [82] and covered the four core areas defined by the OMERACT 2.0 Filter: "death," "life impact," "pathophysiological manifestations," and "resource use/economical impact area" [83]. These items will be rated and ranked by physicians and patients for further inclusion in the core set of outcome measures intended for use in all trials of BD [82].

Summary

The geographic distribution of BD is well characterized with prevalence estimates available for many countries worldwide with high prevalence along the "Silk Road", and the existing data clearly suggest that there is a true geographic impact. Ocular [40–44] and vascular manifestations, some cutaneous lesions such as folliculitis and papulopustular skin lesions, and skin hyperreactivity (pathergy) are more prevalent among men, whereas genital ulcers, erythema nodosum, and joint involvement are more frequent among women. HLA-B51 is the most well-known genetic factor of BD, and alterations have also been described in the oral and gut microbiome profiles of patients with BD. BD is associated with reduced HRQoL, increased morbidity and mortality, more pronounced among male patients. Efforts are underway for the development of validated and widely accepted outcome measures for use in clinical studies of BD.

Practice points

- The prevalence of BD varies substantially worldwide, with the highest estimates observed in Turkey and the Middle East and the lowest in northern Europe. Different types of study designs and sampling strategies may lead to the wide range of prevalence estimates of BD in the same geographic area.
- Ocular and vascular manifestations of BD are more common among male patients, whereas genital ulcers, erythema nodosum, and joint involvement are more common among female patients.
- Patients with BD, particularly young males, have a significantly increased overall mortality compared to the age- and sex-matched general population.

Research agenda

- The role of HLA-B51 gene in the pathogenesis of BD and disease expression has yet to be fully elucidated.
- More studies are needed to assess the possible role of microbiota and other environmental factors in the development and flares of BD. The prospect of identifying specific alterations in the oral and gut microbiome profile associated with BD may in time allow the development of novel prevention and treatment approaches.

Conflicts of interest

I have no conflict of interest.

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