Abstract

Behcet’s disease (BD) is a systemic and inflammatory disorder mainly present along the ancient Silk Road, from Mediterranean Sea to East Asia. A wide range of prevalence figures (0.1-420/100,000) are reported for BD, also among Turkish populations of similar genetic background living in different countries. Recently, a decline of the incidence of BD and a change of the disease spectrum to less-severe manifestations are reported from Japan and Korea, two genetically homogenous, affluent populations with limited immigration. We hypothesize that a decline in infectious diseases, especially dental/periodontal infections, associated with the improvement in oral health, could be a part of these changes in the disease expression. Further epidemiological studies in other populations might demonstrate whether there is a worldwide similar trend and may provide a better understanding of the triggering factors for the onset and course of BD.

Key words: Behcet’s disease, epidemiology, oral health
Introduction

Behcet’s Disease (BD) is a systemic, inflammatory disorder of unknown etiology. It is characterized by oral and genital ulcers, cutaneous, ocular, musculoskeletal, vascular, central nervous system and gastrointestinal manifestations. Behcet’s disease is more prevalent in some regions and populations mainly present along the ancient Silk Road, from Mediterranean Sea to East Asian countries including France, Tunisia, Turkey, Israel, Iran, Korea and Japan (1). BD has a higher prevalence in these countries (2-420 per 100,000) compared to USA and Europe (0.1-7.5 per 100,000). Similarly, a more severe disease spectrum such as ocular, vascular and central nervous system inflammation is commonly observed in these regions. Ethnicity and gender are accepted to be the major factors affecting the prevalence and manifestations of the disease (2). However, environmental factors such as infectious agents (Streptococcus spp, Herpes simplex virus), food, hormones etc. are also implicated in the etiopathogenesis of BD driving pathogenic innate and adaptive immune dysregulation (3-5). However, relative contributions of genetic or environmental factors to disease pathogenesis are still not clear.

About ten years ago, we first suggested that the incidence and severity of BD might be in a decline worldwide (6). In this perspective, we will discuss the recent data on the epidemiology of BD and some the environmental factors associated with epidemiological changes.

Recent epidemiological studies of BD

Recent studies supported the wide difference in BD incidence among different populations (7). One method to investigate the role of genetic vs environmental factors in BD pathogenesis is to assess the prevalence of BD in a genetically homogeneous population living in two different countries. Studies on Turkish population living in Turkey vs European countries are the most comparable for this purpose (1,7), as Turkish population rarely have inter-racial marriage in Europe (app. 5%) (8). The range of BD prevalence in mainland Turkey (Anatolia) is in the range 70-420/100,000 (9). As in a previous study from Berlin (9), Kappen et al. recently demonstrated a low prevalence of BD in Amsterdam region (71/100,000) among the Turkish population (10). However, both of these studies are ‘census
surveys’ which depend on hospital/medical data records, whereas studies performed in Turkey are sample surveys questioning/examining patients directly. Subgroup analysis of 45 reports published between 1974 and 2015 demonstrated a significant difference for prevalence between sample survey design (82.5/100.000) compared to a census design (3.6/100.000). According to metaregression analysis, ‘study design’ is identified as an independent covariate significantly affecting the prevalence of BD. Reflecting this methodological issue, in sample surveys, up to 95% of the cases are newly diagnosed, mucocutaneous-limited cases suggesting that sample surveys perform in general population to detect milder cases which possibly are not present in hospital-based census surveys (7).

With these methodological issues, we previously claimed that the only clear clue whether environmental factors predispose to or modify the disease course can be shown in longitudinal follow-up of BD patients in an ethnically homogenous, non-immigrant population with a stable health reimbursement system covering most of the country population (6). This type of data recently emerged from East Asian countries such as Korea and Japan. In a recent study using the Korean National Health Insurance Claims Database covering over 50 million of the Korean population, Lee et al. observed that the incidence of BD decreased from 7.47/100.000 in 2006 to 2.51/100.000 in 2015 (11).

Although epidemiological, community-based data is not available, recent data from Japan also suggest that the frequency of BD is getting less among hospital-based surveys of uveitis patients (23.2% in 1981-83 vs 6.2% in 2002) with the prevalence dropping to 7.5/1,000.000 in 1990 from 8.9/1,000.000 in 1984 (12-14). The number of new patients in Hokkaido island (served with only one referral uveitis center) was reported to be 83 between 1994-2003 compared to 152 during 1984-1993 (15). The decreasing trend for BD among uveitis patients in Japan continued in a recent series (16). In a series from Taiwan, again with a good reimbursement system, prevalence of BD among non-anterior uveitis patients decreased from 13.3% in 1991-2000 to 9.5% in 2001-2014 (17). On the other hand, BD is still the main cause of uveitis (24.9%) among patients followed-up in tertiary uveitis centers in Turkey (18), however there might be a decreasing trend compared to a decade ago (32.1%) (19).

Another aspect is a decline in the severity of BD in Japan, as the disease is becoming milder with less frequent ocular attacks and vision loss (14). A lower risk of losing vision is also
reported in male patients from Turkey who were diagnosed in the 1990s compared to patients from 1980s (20). A very similar data is also reported from National Eye Institute (NEI)(21). Another trend observed in Japan is the decreasing frequency of ‘complete’ type of BD, associated with less vascular, central nervous system and ocular disease in patients presented after 2008 compared to pre-2000 (22). Similar observations of less-severe uveitis and complete-type BD is also reported from Korea in series followed in 1990s compared to 2000s (23,24). As expected with better health coverage, BD patients are diagnosed earlier and treated better in recent years and the authors usually explain this trend with earlier and more aggressive treatment approaches. However, a similar trend observed in East Asian countries with a stable, good health coverage suggests that the epidemiology might also be changing to a less prevalent and severe disease spectrum for BD.

Environmental factors associated with the change in BD epidemiology

Change of BD incidence in populations such as Japan and Korea which are accepted to be fairly stable in genetic/social factors, can be explained mainly by environmental factors. In this context, association of BD with infections and allergy needs close scrutiny as they might be the two major environmental factors changing in recent years (5).

Oral health as a part of general health is affected by barriers to oral health services and personal risk factors (25) as well as oral ulcer pattern in BD (26)(Figure 1). Therefore, country-based differences might be seen. Recent studies from our group and others have demonstrated that BD patients have a poor-oral health demonstrated by impaired dental and periodontal indices such as caries, loss of teeth and gingival scores (5, 26, 27, 28). However, the main issue in these studies is the difficulty in determining the role of persistant oral ulcer presence on the maintenance of oral hygiene, namely brushing and dental floss practices. In spite of these difficulties, with better statistical approaches G. Mumcu et al. have recently demonstrated that both dental caries and need of tooth extraction as focal infection focus are found to be mediators of disease severity. In addition, male gender as a well-known severity factor is also reapproved in the analysis (29). Oral interventions are also shown to decrease oral ulcer presence in BD patients in a longitudinal 6-month, prospective study (30). Antibiotics such as penicillin (31) and azithromycin (32) are shown to decrease
mucocutaneous symptoms, especially folliculitic lesions and decrease the healing time of oral ulcers and scores of plaque indexes (32). Among other environmental factors smoking, stress, various food associated with histamine release and allergies are implicated as the triggering or suppressing factors for BD incidence and severity (33-35), discussed in more detail elsewhere (5). However, none of these factors can explain the whole spectrum of the changing epidemiology of BD. In conclusion, a decline of BD incidence and a change of disease spectrum to less severe manifestations is reported first from Japan and Korea, but requires confirmation in other populations. If this is a worldwide trend, a better understanding of the environmental etiological factors especially infections associated with the disease onset or relapses may lead the way to new therapeutic approaches for BD, which is still a disease with significant morbidity, mortality and work limitation (36).
Figure 1: Barriers to Oral Health Services and Risk Factors for Oral Health in BD.
References


25. WHO. www.who.int/health-topics/oral-health


