Review

A possible decline in the incidence and severity of Behçet's disease: implications for an infectious etiology and oral health

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ABSTRACT

Behçet's disease (BD) is a systemic and inflammatory disorder mainly present along the ancient Silk Road, from the Mediterranean to East Asia. A wide range of prevalence figures (0.1–420/100.000) are reported for BD, also among populations of similar ethnicity living in different countries. Recently, a decline of the incidence of BD and a change of the disease spectrum to less severe mucocutaneous manifestations is reported from Japan, a genetically homogenous, affluent population with limited immigration. Among environmental factors, a change in atopy/allergic disorders and a decline in infections are two possible mechanisms for this epidemiological change. A shift in Th1/Th2 immune balance towards Th2-associated immune responses are possible, however "hygiene hypothesis" associated with this approach does not explain the recent trend of the increase in Th1-associated disorders such as inflammatory bowel disease and multiple sclerosis in Western Countries. We hypothesise that a decline in oral infections, associated with the improvement in oral health in Japan, could be behind this decline. Better epidemiological studies in other populations will show whether this decline is a worldwide trend and may provide a better understanding of the environmental factors associated with the onset or relapses of BD, leading a way to new therapeutic approaches.

1. Geographic distributions and ethnic differences

Behçet's disease (BD) is a systemic, inflammatory disorder of unknown etiology. It is characterised by oral and genital ulcers and cutaneous, ocular, arthritic, vascular, central nervous system and gastrointestinal involvements (1). Clinical manifestations affect also the quality of life in BD (2). Oral ulcer, the cardinal clinical symptom, is the first manifestation in the majority of patients with BD (1).

Behçet's disease is more prevalent in some regions and populations mainly present along the ancient Silk Road, from Eastern Mediterranean to East Asian countries including 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 (1, 3). Ethnicity and gender are accepted to be the major factors affecting the prevalence and manifestations of the disease. Infectious agents (Streptococcus spp, Herpes simples virus), genetic factors (human leukocyte antigen (HLA)-B*51), hormones and innate and adaptive immune disregulation are implicated in the etiopathogenesis of BD (4). However, relative contributions of genetic or environmental factors to disease pathogenesis are still not clear.

The most controversial data for the prevalence of BD come from Turkey where a range of 20–420 per 100.000 is reported (5, 6). However, except one study in Trace region which is the European part of Turkey (20/100.000) (7), all other studies report a range of 80–420 per 100.000 (8-10). Ethnic differences inside Turkey can be crucial, as Armenians living in Istanbul had a lower prevalence of BD compared to the Turkish population of the same city (11). On the other hand, in BD patients of Turkish origin living in Berlin most recent prevalence is reported to be 77 per 100.000 and seems lower compared to mainland Turkey (12). This obser-

vation, pointing to an environmental change, has recently been observed for another common genetic disease of Middle-Eastern populations, Familial Mediterranean Fever, which is reported to have a milder course in Turkish patients living in Germany compared to mainland (13). A lower prevalence of BD is also reported in Japanese population immigrated to Hawaii (14).

A recent report from France confirmed previous observations of a "south-north" gradient of BD with a higher prevalence in southern European and North African countries (6). In this study, a prevalence of 2.4/100.000 was reported in patients of European ancestry and fit within the range of 1.5–7.5 reported from Southern Europe. The reported rates of patients of North African (34.5) and Asian (17.5) descent in the same study are also roughly similar to 7–20 per 100.000 from Egypt, Iraq and Saudi Arabia. The authors suggest with this data that a sustained high prevalence of BD among those who immigrated from high-risk to low-risk areas is strongly in favour of a "hereditary" rather than an "environmental" basis for BD. However, we think it is still premature to suggest that environmental factors have a limited role in disease pathogenesis. 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. This type of data has recently emerged from Japan.

2. A possible decline in the incidence and severity of BD in Japan

Although epidemiological, community-based data is not available, recent data from Japan suggest that prevalence of BD is getting less among hospital-based surveys of uveitis patients (23.2% in 1981–83 *vs*. 6.7% in 2003) with the prevalence dropping to 7.5/100.000 in 1990 from 8.9/100.000 in 1984 (15-17). The number of new patients in Hokkaido island (served with only one referral uveitis centre) was reported to be 83 between 1994 and 2003 compared to 152 during 1984-1993 (18). Although, this decline is not accepted by all Japanese authors, the prevalence of BD reported by them is similar to other series in recent years (5.8%) and lower compared to sarcoidosis and Vogt-Koyanagi-Harada disease which overtake BD as the most frequent cause of uveitis in Japan in recent years (19). On the other hand, BD is still the main cause of uveitis (32%) among patients followed-up in tertiary uveitis centres in Turkey (20). Similarly, no change in the number of new patients is reported from a tertiary referral centre in Taiwan among Chinese BD patients (21).

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 (17). 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 (22). A very similar data is also reported recently from National Eye Institute (NEI), US (23). The authors prefer to explain this trend with more aggressive treatment approaches. However, reports of only cross-sectional, hospital-based surveys without a national database in countries like Turkey or data of tertiary Institutes like NEI preclude us from commenting definitely on this issue. As expected with better health coverage, BD patients are diagnosed earlier and treated better in recent years. However, also due to this better care, the number of new cases reaching to tertiary care centres such as NIH or University Hospitals in Turkey might change and be biased towards more severe or complicated cases, hiding the evolving nature of disease epidemiology. In a tertiary centre from Taiwan mean time to vision-loss decreased and average time between the disease onset and first visit increased in recently treated patients. As an explanation for this paradoxical observation, the investigators suggest that patients with more severe disease are preferentially referred to their centre in recent years (21).

Finally, an important, other possible factor for the changing epidemiology may be role of the socio-economical status. Behçet's disease seems to be related to lower socio-economical status in Turkey, which still has a large income gap. In this context, in a study from Turkey investigating the socio-economical status, BD patients are observed to have a lower monthly family income, wealth score and education with higher unemployment compared to ankylosing spondylitis and inflammatory bowel disease (IBD) patients (24).

3. Enviromental factors and "hygiene" hypothesis

As Japanese population is accepted to be fairly stable in genetic background with a standard health care covering all of the Behçet's population, a decline in BD incidence and severity can be explained 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 Japanese environment.

Protective effect of infections *(hygiene hypothesis)* will be first discussed in this context. This notion which was first developed for allergic diseases may be applied to other autoimmune and inflammatory disorders of unknown etiology such as BD (25). Hygiene hypothesis is first related to Th1/Th2 paradigm which accepts a balance between immune reactivity for Th1 related disorders (most commonly infections and auto-immune disorders) and Th2 type allergies (26, 27). Japan is one of the countries with an increasing incidence of atopic disorders, especially in childhood. Exposure to a Th2 type cytokine mileu might suppress Th1 responses and childhood exposure to infections have been suggested to be crucial to prevent the development of Th2-associated atopy in later ages. A negative association between the incidence and severity of BD and atopy seems also possible. Atopic disorders, serum IgE and peripheral blood eosinophil measurements are shown to be lower in BD patients from Korea (28). We also observed a negative association of disease severity with the presence of atopy in BD (29), on the other hand, dermographism is found to be increased in another study without a change in serum atopy markers (30). However, a problem with this hypothesis is the recent trend in the incidence of

Th1-associated autoimmune diseases in Western countries. Incidences of type-I diabetes, IBD and multiple sclerosis, all presumed to be Th-1 associated disorders, has been steadily increasing in recent years in North America and Europe (25, 26). Such a trend is possibly not explained by genetic differences as children recently immigrated to Western countries also has the incidence of the immigrated country such as the UK (31). So it seems that infections protect against both Th1 and Th2-type disorders. In this context, BD with its features of both autoimmune responses and auto-inflammatory features of innate activation may have a different association with infections, not typical for "hygiene" hypothesis (32).

4. Can a decline in infections protect against BD?

Infections are suggested to have a major role in the induction of both allergy and autoimmunity (33). An infection-associated pathogenesis of BD is also long been implicated (34). A possible source of infection in BD is pustular skin lesions which are shown to be non-sterile (35). Although a wide variety of organisms such as S. *aureus, Propionibacterium acnes* and coagulase negative staphylococcia are cultured from BD lesions, gram-negative microorganisms such as *E. coli* and *Prevotella* species were also suprising highly present when compared to acne vulgaris. An interesting association in this context is acne presence in BD associated with arthritis, resembling SAPHO syndrome (36). Although not proven, SAPHO syndrome is accepted to be a reactive infectious osteitis in geneticall-ly predisposed subjects (37). Arthritic symptoms of BD might also respond to anti-bacterial treatment (38).

Dental and periodontal health as a foci of infection is an integral part of general health. Oral health plays a critical role in chronic systemic conditions regarding cardiovascular diseases, respiratory disorders, and diabetes (39). Since clinical manifestations start most commonly from oral mucosa, oral microbial flora is also suggested as an initiating factor of BD (4, 34, 40). Most-commonly investigated microorganism for the pathogenesis of BD is streptococcia among oral flora. Colonisation of streptococcia on oral mucosa can trigger the immune responses for ulcer formation (40, 41). The close relationship between streptococcal infections and BD is also supported with clinical observations such as a higher incidence of infections such as tonsillitis and dental caries, aggravation of the disease by dental treatments (42-44) and the beneficial effect of antibacterial treatments on mucocutaneous symptoms (45-47). Poor dental and periodontal health, affecting oral quality of life, is reported in patients with BD, especially in a clinically severe subset, with an associated, increased dental plaque accumulation (48, 49). In addition, an increase in the number of extracted teeth, probably related to dental or periodontal infections, is observed in BD patients (34). The relationship between oral health and ulcer formation could be explained by microbial factors. Chronic foci including poor oral health and the presence of oral infection may trigger oral ulcers in BD patients (34, 48, 50, 51). Oral streptococci can colonise and penetrate the oral mucosa (43, 45, 52). S. sanguis is shown to adhere to buccal epithelial cells and cause to local inflammatory cytokine responses in germ-free mice model (43). Increases in Toll like receptor-6 (TLR-6) expressing granulocyte population as a part of innate immune response was also observed after S. sanguis stimulation (53). In addition, TLR can recognise lipoteichoic-acid localised in gram-positive bacteria cell wall and stimulate immune responses in BD (54). "Molecular-mimicry" due to cross-reactivity between heat shock protein-65 (HSP-65) of S. sanguis and human HSP-60 is suggested to be another mechanism of ulcer formation (55). Therefore, presence of infection foci and poor oral health might activate immune responses in BD.

In this context we can assume that the decline in the incidence and severity of BD might be associated to a decline of infections in Japan. Among various infectious focuses, oral microbiata is possibly the most relevant. Data for upper respiratory tract infections, pharnygitis and tonsillitis is limited, but is known to be less severe in recent years in all countries. However, dental health data have more interesting clues for BD. Less caries and decay/missing/filled tooth (DMFT) scores reflecting caries experience are reported from Japan in recent years. In Japanese population, the mean DMFT score was 15.2 in people aged between 35-39 in 1999 and 14.2 in 2005 (56). According to DMFT scores in 2005, the mean scores of decay teeth, missing teeth and filled teeth were 1.5, 1.0 and 11.7, respectively. These scores got progressively better in recent years. In Turkish population, the mean DMFT score was found to be 11.6 in population aged 35–44 years old in 1988 and 12.6 in 2001-02. The mean scores of decay teeth, missing teeth and filled teeth were 1.4, 7.9 and 3.4, respectively in the 2001–2002 period (57). The major component of the DMFT score was the number of filling teeth in Japan in contrast to decayed teeth in the Turkish population, reflecting better access to dental treatments in Japan. According to "Healthy Japan 21" project, improvement of dental health is the one of nine specific areas regarding diet and nutrition, physical activity and exercise, leisure and mental health, smoking, alcohol, dental health, diabetes, cardiovascular disease, cancer (58). Therefore, an increase in number of filled teeth could be predicted in Japanese population also in the future.

An interesting aspect of this approach is the link between oral infections and allergy. An inverse relationship between periodontitis and allergy is previously shown (59). As periodontal health is getting better in Japan (60), this might be linked to less microbial exposure and more atopy leading to the suppression of Th1 responses required for developing BD in genetically susceptible individuals.

Approach to oral infections in BD might also change with better understanding of their role in pathogenesis. We had recently shown that elimination of oral infection foci with dental and periodontal treatments decrease the number of oral ulcers, at least in a 6-month, short-term follow-up (61). Similarly, renal attacks of Henoch-Schonlein Purpura, a systemic vasculitis most common in

children and adolescents and is associated with upper respiratory tract infections, also decrease after early dental and ENT treatments (62).

Finally, links between infection and autoimmune and autoinflammatory responses can be more complex and associated with the clearance deficiencies which seem to have a major role in autoimmunity (63). As neutrophils arrive very early to initiate inflammation in tissues and live too briefly, clearance of apoptotic material by complement system proteins such mannose-binding lectin (MBL) is critical in suppressing inflammation. An adaptive response related to neutrophils in BD may be promoted by insufficient phagocytosis of apoptotic neutrophils by dendritic cells. In this context, serum MBL levels are shown to be decreased in BD patients and MBL deficiency may prolong the exposure of neutrophil-related antigens to adaptive immune system (64). A lower bacterial clearence due to low MBL levels may also predispose to bacterial infections and a higher prevelance of *S. mutans* colonisation is observed in patients with low MBL levels in BD (65).

5. Conclusion

A decline of BD incidence and a change of disease spectrum to less severe manifestations is reported from Japan, but requires confirmation in other populations. If this is a worldwide trend, a better understanding of the environmental etiological factors *(allergy or infections)* associated with the disease onset or relapses may lead the way to new therapeutic approaches for BD. In this context, we suggest that improvement of oral health and elimination of infection foci should be a first-line approach, in addition to standard medical treatment in BD patients.

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