Review

Behçet's disease: a dentist's overview

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Introduction

Behçet's disease (BD) is a multi-systemic inflammatory disease characterized by oral and genital ulcers, and cutaneous, ocular, arthritic, vascular, gastrointestinal and central nervous system manifestations (1-3). In this review, oral involvement as a part of the clinical spectrum is discussed within the perspective of dentistry according to its interactions with the etiopathogenesis, immune response, treatment protocols, disease activity and quality of life in BD.

Oral involvement in the clinical spectrum

Oral ulcers categorized as major, minor and herpetiform are a common clinical condition. They constitute the first clinical presentation in the majority of patients with BD. Oral involvement is deemed to be present in BD when oral ulcers are observed by the physician or patient at least 3 times in the course of a year (4). According to the International Study Group (5), recurrent oral ulceration and the presence of two other criteria including recurrent genital ulceration, eye lesions, skin lesions, and positive pathergy test are necessary for the diagnosis/classification of BD.

The relationship between oral health and etiopathogenesis

Infectious agents (*Streptococcus* spp, Herpes simplex virus), genetic factors (HLA-B51), hormones and immune disregulation are implicated in the etiopathogenesis of BD (1-3). Infections may be a crucial component of BD as an initiating and/or activating factor. The role of streptococci as an infectious agent is being extensively investigated in the pathogenesis of BD. The increased incidence of tonsillitis and dental caries, aggravation of the disease by dental treatment (6-13), and the beneficial effect of antibacterial treatments on symptoms (11, 14-16) are important clinical observations pointing to a relationship between streptococci and BD in previous studies.

In the immunopathogenesis, an abnormal hypersensitivity to streptococcus-related antigens is observed in the peripheral blood mononuclear cells (PBMC) of BD patients. When stimulated with streptococcal antigens, increased production of interleukin-6 (IL-6) and interferon-alpha (IFN-γ) are observed in the PBMC of patients with BD. Similarly, superantigens such as *E. coli*- and *S. aureus*-derived antigens could also stimulate the production of these cytokines from PBMC in BD (1, 11).

Oral microorganisms such as streptococci colonize in the oral cavity and can trigger an immune response for ulcer formation in BD (17, 18). The colonisation of streptococci, antigenic mimicry between the microbe and the host causing an abnormal response to microbial antigens with cross-reactive tissue antigens, and genetic factors leading to an aberrant immune response are crucial items in the occurrence of oral ulcer. Inflammatory cytokines such as IL-2, IL-6, IFN-γ and TNF-α were observed in the oral tissues of germ-free mice infected with *S. sanguinis* (12). Moreover, Bes-1 DNA and heat shock protein-65 (HSP-65) derived from *S. sanguinis* were detected by polymerase chain reaction (PCR) and PCR-*in situ* hybridization in mucocutaneous lesions (13). In a previous study we also found the number of oral ulcers to be associated with higher *S. mutans* levels ($\geq 10^5$ CFU/ml of saliva) in BD patients. An increase in the colonisation of *S. mutans* might predispose to the extended presentation of exogenous antigens to the host (17, 18).

Oral health forms a part of a person's general health (19) and a linkage between infectious foci in the oral environment and various disorders such as

cardiovascular disease (20-22), diabetes mellitus, pre-term low birth-weight babies, and chronic obstructive pulmonary disease (23) have been reported (19, 21). Similarly, oral health problems are observed more frequently in patients with BD (24-28). Poor dental and periodontal health leading to increased microbial plaque accumulation, gingival inflammation, probing depth, and number of extracted teeth have been observed in patients with BD and recurrent apthtous stomatitis (RAS) compared to healthy controls. The increase in microbial dental plaque accumulation is related to the presence of oral ulcers and has been reported to be a significant risk factor for an increased severity score in patients with BD (24). Our results are confirmed by Akman *et al*., who showed an impaired periodontal status in BD patients that was associated with disease severity (27). In addition, an IL-1 associated single nucleotide polymorphism, which might predispose to the occurrence of both periodontitis and BD could affect this process by activating a periodontitis-induced autoinflammatory response (28).

Recently a prospective clinical study was conducted to examine the interactions between oral health and BD. Dental and periodontal treatments were administered to 29 patients without modifying their systemic treatment modalities. After the elimination of infections through these treatments, patients were followed up for 6 months. Two crucial findings were obtained from this clinical study. First, oral ulcer activation was seen in patients within the first 2 days of dental treatment, without a systemic activation. However, the number of oral ulcers significantly decreased within the following 6-month observation period compared to the pre-treatment period. Therefore it can be concluded that while dental and periodontal treatment may lead to an activation of oral ulcers in the short term, the elimination of chronic oral infectious focus can improve the prognosis of patients with BD in the long run (29).

Oral health is affected by oral hygiene habits, health beliefs, and dental service organisations (30). Oral health conditions in BD patients were compared recently in two separate populations – Turkey and the United Kingdom (UK). Poor oral health, lower utilisation of dental services, and infrequent tooth brushing were reported in patients from Turkey compared to those in the UK (31).

The role of salivary immunity

The oral cavity is a unique environment because saliva, the epithelial surface layers and polymorphonuclear leukocytes (neutrophils) all contribute to the maintenance of oral health. Antimicrobial peptides produced by epithelial cells and neutrophils form part of the innate immune response in the complex oral environment. The levels of salivary human neutrophil peptides 1–3 (HNP 1-3) produced by neutrophils were observed to be higher in patients with BD. In addition, levels of salivary LL-37 (derived mainly from epithelial cells) and S100 also seem to be higher in BD patients. HNP 1-3 levels were also associated with a more severe disease spectrum (32). Moreover, the levels of S100 secreted by neutrophils (33, 34) was correlated with the frequency of oral ulcers and the plaque index score, reflecting microbial plaque accumulation. The elevation of both LL-37 (32) and HNP 1-3 and S100 (33, 34) reflect the contribution of local and innate immunity in BD.

Growth factors are also important in terms of wound healing and the regulation of inflammation. In BD salivary vascular endothelial growth factor (VEGF) levels were observed to be higher in patients with active oral ulcers. In contrast, epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) failed to increase in patients with active oral ulceration. Paralleling this, EGF receptor expression was found to be higher during remission. Alongside microbial infections, these factors could affect complex wound healing in active oral ulcers (35). In addition to all of these variables, inflammatory cytokines in the saliva may reflect disease activity and help us to understand oral immunity in BD. When the effect of saliva on the cytokine production of PBMCs was examined, an increase in IL-8 production was seen in active BD. IL-1 and IL-6 production could also be stimulated by saliva in BD, although without a difference between active and inactive patients (36).

The effects of treatment modalities on oral ulcers

The optimal treatment protocol for mucocutaneous Behçet's disease is still unclear. Although not yet confirmed in a prospective, controlled trial, with its safe side-effect profile colchicine is still widely used in basic treatment protocols for the mucocutaneous manifestations of BD (37). High-dose corticosteroids and cyclophosphamide or azathioprine as immunosuppressives can control flare-ups in active disease (4). Thalidomide can also eliminate oral ulcers effectively (38). In addition, anti-TNFα and interferon-α therapies may be required for remission in cases of major organ involvement that prove unresponsive to conventional therapies, and they could also eliminate oral ulcer attacks in BD (39). However, their high toxicity does not justify their use to treat oral ulcer activation alone. In our prospective cohort treated with colchicine, the mean number of oral ulcers at baseline was found to be similar to that of the control subjects after 6 months, suggesting the limited role of colchicine treatment (40). In another study the combination of colchicine (1.5 mg/day) and benzathine penicillin (1.2 million units/month) was observed to be more effective than colchicine alone in the treatment of oral ulcers (14).

In a previous study, a short, 4-week course of azithromycin (1500 mg/week) for folliculitic lesions was investigated in a small group of BD patients. A decrease in both the duration of oral ulcers and microbial plaque accumulation was seen during the treatment period (15). Similarly, oral minocycline treatment for 3 months had a modest effect on the elimination of oral ulcerations (11).

When the pattern of oral ulcers was examined in two different patient groups, the number of ulcers was found to be higher in the UK compared to Turkey. Moreover, oral ulcers were more active in UK patients under immunosuppressive treatment than in patients treated

with colchicine in Turkey (31). In contrast, the disease severity score was similar in both patient groups, suggesting that the clinical spectrum may vary with ethnic background in BD. All the same, a patient referral bias to clinical centres between the two countries cannot be ruled out.

Applying more effective treatment protocols for the prevention of oral ulcers could also help to improve oral health in BD. Topical sucralfate solution (41), *Lactobacilli* lozenges (42), and topical granulocyte colony-stimulating factor (43) are some agents that have shown efficacy in the treatment of oral ulcers.

Oral ulcer activity

BD is a multi-systemic disorder and there is no specific laboratory test for the evaluation of disease activity (44). Disease activity indices have been developed to fill the gap, and they include items regarding oral involvement; oral ulcer activity is taken into consideration in the Behçet's disease current activity form (BDCAF) (45) and in the total activity index (46, 47). The presence or absence of oral ulcers (45, 46) and the duration of oral ulcers (44) can be evaluated by these methods. However, ulcer-related outcomes including pain and functional disability are not sufficiently evaluated by these forms.

Alternatively, an organ-specific approach for the different manifestations of BD could be more productive (45). We therefore developed, proposed and validated a Composite Oral Index – including the number of oral ulcers, pain and functional status – to monitor the clinical manifestations affected by oral ulcers (48).

Oral health and quality of life

The effect of disease on the quality of life is widely evaluated in dentistry. Oral health-related quality of life (oral QoL) as a patient-centred outcome measure yields important information regarding the effects of disease on a patient's life. The presence of oral ulcers and ulcer-related pain has been shown to negatively affect oral function and lead to a poor oral health-related quality of life in patients from Turkey (49, 50) and the UK (31). Female gender and treatment with colchicine are the other domains of poor oral QoL (49). Moreover, a similar impairment in oral QoL was observed in both UK and Turkish patients with active oral ulcers (31). Therefore, oral QoL could represent a suitable standard method for the evaluation of patients in clinical studies in different countries.

Conclusion

The environment of the oral cavity has a significant impact in the etiology of Behçet's disease. The presence of recurrent oral ulceration has great importance in terms of the diagnosis, and assessing disease activity and the quality of life in BD. Therefore a dental approach to oral health should form a key component in the clinical evaluation of BD patients. Since oral health can affect disease severity, the elimination of oral infection foci could help to improve the prognosis. Moreover, the properties of saliva should also be investigated more thoroughly to shed light on the relationship between oral infection foci, oral ulcer activity, and disease severity.

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