

The impact of environmental factors on aetiopathogenesis and clinical manifestations of Behçet's syndrome

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ABSTRACT

Behçet's syndrome (BS) is a rare multi-system vasculitis involving blood vessels of any size. BS aetiology is still unclear to date, and the heterogeneity of clinical expression among ethnics and genders make early diagnosis challenging. However, so far, considerable efforts have been made toward the understanding of BS, leading researchers to agree that the coexistence of some environmental triggers and a genetical susceptibility both underlie BS aetiopathogenesis. In particular, viral agents, oral microbial flora, and mucosal microbiota have been widely explored in this regard, but still no specific microorganism has been definitely linked to the disease aetiology. Likewise, the concept that some environmental factors may play a role in BS clinical presentation has emerged based on the growing evidence that disease severity is usually higher in male patients, and that diet and fatigue may be involved in disease recurrence, especially in mucocutaneous manifestations. Moreover, smoke cessation is acknowledged as a risk factor for oral ulcerations, although the underlying mechanism is still not clear. All those environmental factors play their effects through epigenetic mechanisms. The aim of this review is to discuss the evidence on the role of environmental factors in BS aetiopathogenesis and clinical course.

Introduction

Behçet's syndrome (BS) is a rare multi-system vasculitis affecting blood vessels of any size. Clinical hallmarks are oral and genital ulcerations, which commonly represent the onset manifestation, followed by skin papulopustular lesions and recurrent uveitis (1, 2). Less frequent, but more severe

and often organ-threatening are neurological, gastro-intestinal and major vascular involvement. BS prevalence varies according to geographical location, with the highest incidence in the Mediterranean, the Middle East and Far East Asia. Both genders are equally involved, and every age can be affected, but disease typically appears between the third and fourth decade (3).

BS aetiopathogenesis is not clarified. Current knowledge suggests that some environmental factors may trigger disease in genetically susceptible individuals (3-5). The genetic contribution is provided by the well-known association between BS and the allele of the major histocompatibility complex (MHC) locus HLA-B51 (6). However, a stronger association with this locus was described in endemic areas for the disease, and several studies showed an intermediate risk for developing the disease in individuals from endemic areas who have immigrated to non-endemic areas (3, 7). These observations suggest that also the environmental contribution may be fundamental in BS pathogenesis, and it has been postulated that several microorganisms trigger BS. Moreover, environmental factors and lifestyle have recently been a subject of interest concerning their impact on disease activity. Indeed, environmental factors have been linked to clinical relapses (8, 9), suggesting that they might contribute to the well-known impairment of quality of life in BS patients (10). This review aims to analyse and discuss the role of environmental factors in the frame of BS aetiopathogenesis and clinical course.

Infections and microbiome

Hulusi Behçet first suspected that an infectious agent was related to the aeti-

ology of BS (11). Since then, many microorganisms have long been proposed as possible trigger of disease, especially *Herpes Simplex Virus* (HSV)-1 and Streptococci. To date, the most accepted theory to explain the role of infectious agents in BS aetiopathogenesis is the high homology between some microorganism antigens and human proteins, like heat shock proteins (HSP), and the resulting cross-reaction leading to an immune response in genetically predisposed individuals (3, 4, 12).

Already in the 1980s, HSV-1 DNA was detected in peripheral blood mononuclear cells (PBMCs) of BS patients (13), and the presence of part of the virus genome in these cells was later confirmed using DNA-RNA hybridisation techniques (13, 14). Later, polymerase chain reaction (PCR) studies showed a significantly higher presence of HSV-1 DNA in peripheral blood leucocytes of BS patients than in healthy controls (HCs) (15). PCR also identified increased positivity of HSV-1 DNA in saliva, genital ulcers and intestinal biopsy specimens (13, 16). Moreover, a BS-like animal model was developed by inoculating HSV-1 in imprinting control regions (ICR) in mice (4, 17, 18), which developed BS-like symptoms such as oral, genital and skin ulcerations, uveitis, arthritis and gastrointestinal ulcers. Since then, this animal model has been consistently used with the aim of testing the therapeutic efficacy of some drugs. For example, famciclovir was administered to these mice and the improvement of some BS-like symptoms was obtained (19). Of note, a previous randomised controlled study (RCT) failed to show an effect of acyclovir in BS patients (20). In conclusion, the overall current knowledge allows us to speculate that active HSV-1 infection alone cannot explain the association between the virus and BS, and that an altered immune response to the viral agent is also needed.

Parvovirus B19 has been implicated in the aetiology of vasculitis and other rheumatic conditions (21). Regarding BS, Baskan *et al.* (22) detected higher proportions of B19 DNA in non-ulcerative skin lesions of patients compared to controls, suggesting a

causal relationship between the viral infection and the disease. Nonetheless, subsequent studies could not establish a certain correlation as resulted by the absence of statistically different serological response to the infection in BS patients *versus* HCs. In addition, no correlation was found between the presence of anti-B19 IgM and the clinical presentation (23, 24).

The association between BS and *Helicobacter Pylori* (*H Pylori*) was studied by several groups (25-27) but the results were ambiguous. A meta-analysis was conducted in 2019 (28) showing that overall *H Pylori* infection is more frequent in BS patients than control populations, and that infection eradication would improve BS clinical presentation. However, further research is needed to verify these findings.

Since oral ulcerations are the main manifestation in BS, it has been long speculated that the oral microbial flora may be involved in the pathogenesis of the disease (29). BS patients were reported to have a higher incidence of chronic tonsillitis and dental caries compared to controls (13, 30), and exacerbation of both cutaneous and systemic symptoms was observed after dental procedures (29, 31). Interestingly, some authors indicated that periodontal therapies may decrease the number of oral ulcers in long-term follow-up (31), and that improvement of oral health results in a better course of disease (29, 32). As a result, Streptococci were the most studied bacteria in BS as they are the prominent component of oral cavity flora, and particularly some *Streptococcus* (*Str*) *Sanguinis* strains were isolated from oral ulcers in BS patients (33). In addition, serum antibodies against some *Str Sanguinis* strains were found to be higher in BS patients than in healthy controls (34).

Other studies focused on the presence of bacteria in BS skin lesions. Pustular lesions in BS are not sterile, and microorganisms found in these lesions are different from those of common *acne vulgaris* (13, 35). This may explain why papulo-pustular lesions in BS patients occur in unusual sites for acne, such as arms and legs. Moreover, it was shown that both mucosal and

non-mucosal BS manifestations may be induced by the skin injection of *Str pyogenes*, *Str viridans*, *Str haemolyticus* and *Str faecalis* (36). Overall, all the previous observations regarding Streptococci may be interpreted as the consequence of the immunological response to antigens derived from Streptococci which enter the blood circulation (13). The underlying mechanism for such a process is still unknown, but it is assumed that a chronic streptococcal focus may eventually result in the development of hypersensitivity in BS patients, namely an abnormal immune response occurring after stimulation with streptococcal antigens (13, 36).

To date, it is assumed that oral and gut microbiome peculiarities participate in the aetiopathogenesis in BS. A general reduced bacterial diversity (37) and high variance in abundance of several bacterial species was described (38-41). Ulcers apparently show different bacterial colonisation in oral and genital mucosa, and the microbial community in both oral and genital mucosa possibly vary according to disease activity. For example, an oral microbiome study from the UK showed that *Str salivarius* and *Str. sanguinis* were highly colonised in oral ulcer sites in active patients compared to inactive patients (41). Moreover, Ogunkolade *et al* (39). found that *Staphylococcus spp.* was more present in ulcerated samples compared to non-ulcerated samples in BS patients.

BS patients also show low biodiversity and a distinct fingerprint in gut microbiota composition (37, 40). Many authors reported decreased butyrate-producing bacteria (BPB) in patients' fecal samples (37, 42, 43). It has been suggested that the reduction of butyrate is responsible for the upregulation of T helper (Th)-17 cells and down-regulation of T regulatory (Treg) cells (44). An RCT by Emmi *et al.* (45) assessed the effects of butyrate-enriched diet, which reduced leukocyte Reactive Oxygen Species (ROS) production and improved plasma total antioxidant capacity after three months in BS patients. Interestingly, they did not find any differences in gut microbiota, suggesting the necessity for a longer nutritional intervention. Lastly, the evidence that different disease

manifestations are linked to variable relative abundance of some bacterial species in stool samples suggests a possible role of microbiome in BS clinical presentation (43).

In conclusion, no infectious agent has been isolated as the specific aetiological agent of BS. Although it is unlikely that a microorganism or microbiome is sufficient to explain BS alone, there is general agreement that they play a triggering role through an altered immune response in susceptible individuals.

Diet and supplements

Recently, growing scientific interest has focused on the role of diet in rheumatic diseases, suggesting its contribution to the pathogenesis and prognosis of these conditions (46, 47).

Although food is mentioned as a potential risk factor of BS recurrence, there is no exhaustive literature about potential mechanisms involved. The possible relation between food and aphthous ulcers recurrence in BS patients has been investigated through submitted questionnaires in three studies (8, 48, 49). These studies concluded that food is a possible trigger for oral ulcers, however, the foods the patients mentioned were different in the studies. Eggplant (8, 49) and nut (48) were the most frequently reported as associated with the presence of oral ulcers, followed by walnut, melon, sodas, tomato, hot pepper, and others (8, 49). This heterogeneity could be explained by the different cultural and socio-economic factors of the countries where the studies were conducted, but sourness seems the common chemical characteristic of triggering foods linked to oral ulcers recurrence (48). However, it has been proposed that histamine, a pro-inflammatory mediator which stimulates the immune system, may be the link between these foods, as most of them are histamine-rich or histamine-releasing (48).

Supplements have been investigated as a protective factor with an anti-inflammatory role. An RCT evaluated the role of zinc in patients with BS. Zinc suppresses NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome, whose priming determines the activation of interleukin (IL)-1 β and

IL-18, through its antioxidant effects. The authors found that zinc gluconate (at the dosage of 30 mg/day) led to an improvement in genital and oral ulcers and to significantly reduce NLRP3 in the blood samples of patients *versus* the placebo group over 12 weeks. Interestingly, they did not find an effect on other disease manifestations (50).

Curcumin is a natural polyphenol known for its immunomodulatory and anti-inflammatory properties via the cyclooxygenase-2 (COX-2) pathway inhibition and nuclear factor- κ B (NF- κ B) activation. Recent reports have indicated beneficial effects of curcumin in various autoimmune inflammatory diseases (51). Given its low bioavailability in human body, nanoparticles represent a useful tool to improve curcumin solubility. Therefore, 80 mg nanocurcumin capsules were given daily to BS patients for 8 weeks in an RCT assessing the effects of nanocurcumin supplementation in BS (52). At the end of the study, the authors found an increased frequency of Treg cells and increased serum levels of Transforming growth factor (TGF)- β and IL-10 in the nanocurcumin group *versus* the placebo group. Moreover, the BDCAF (Behçet's Disease Current Activity Form) was significantly decreased in the nanocurcumin group. This could be explained by the capacity of curcumin to control T cell proliferation and proinflammatory cytokine expression. Other RCTs are now in progress to elucidate the role of supplements and food in BS activity, with the aim of finding new possible therapeutic molecules of the disease (53).

Tobacco smoke

Smoking clearly has a negative effect on medical health and on autoimmunity (54). However, several studies in the previous years reported a protective effect towards recurrent oral ulcerations (ROA) and aphthosis in BS (55-60). The first evidence regarding the association between smoking and ROA date back to the past century, when this condition was reported as being more common in non-smokers than smokers (55, 56), and improved by smoking resumption (57). Later on, ev-

idence emerged that nicotine assumption overall improved oral aphthosis in BS (59, 61, 62), as already previously stated by Axéll & Henricsson *et al.* as regards ROA (58). Moreover, the latter study also found a lower frequency of oral ulcers in heavy smokers compared to light smokers. Smoking was also identified as preventive towards genital ulcerations and other mucocutaneous manifestations of BS (59, 63).

The mechanism responsible for the favourable effects of smoking on BS are not fully clarified, but it was observed that nicotine reduces *in vitro* pro-inflammatory cytokines production by keratinocytes and dermal microvascular endothelial cells, suggesting an anti-inflammatory effect as a possible explanation (64, 65). Moreover, biochanin A is likely to show a further anti-oxidant strength, alone and in combination with nicotine.

Of note, not all authors agree on the beneficial effects of nicotine. Indeed, Aramaki *et al.* (66) indicated that smoking may be a risk factor for chronic progressive neuro-BS (66), and Lin *et al.* (67) reported a 2.2-fold higher risk of all types of uveitis in smokers *versus* non-smokers in a retrospective case-control study. In a cross-sectional study evaluating the effects of smoking on a Korean BS population, gastrointestinal and vascular manifestations were significantly higher in smokers than non-smokers (68). Lastly, Malek Mahdavi *et al.* (60) observed a higher overall disease activity in smokers and ex-smokers compared to patients who had never smoked.

Finally, it should be mentioned that toxic by-products of tobacco smoke contribute to air pollution which is assumed to promote oxidative stress and systemic inflammation. In fact, it has been shown that exposure to air pollution increases the levels of tumour necrosis factor-alpha (TNF- α), IL-6 and IL-1 β *in vitro* and *in vivo* in a dose-dependent manner. These cytokines are known to promote systemic inflammation possibly leading to autoimmune diseases (69-71). A recent retrospective observational study found that the increased presence in the environment of methane (CH₄) and total hydrocarbon

(THC) was correlated to an augmented risk of developing uveitis (72). In conclusion air pollution could be related to the development of autoimmune diseases, but further studies are needed to unveil the role of air pollution in BS.

Hormonal factors and stressors

Several studies have investigated the role of hormones in BS, the results of which were discordant regarding sexual hormones and hypothalamic-gonadal axis in female patients. In particular, Anti Mullerian Hormone (AMH), Follicle-stimulating Hormone (FSH), Luteinising Hormone (LH), and Oestradiol (E2) levels do not seem to be correlated to disease activity nor to disease duration (73, 74). However, menstruations were reported as triggers for BS skin and mucosa lesions (9, 75). In contrast with the evidence of the anti-inflammatory effects of testosterone in other rheumatic diseases (76), testosterone in BS male patients may influence neutrophil activation and polarisation in a Th-1 type immune pattern which leads to the production of IL-2 and IL-12 and downregulation of IL-10. This might explain the increased severity of disease in male BS patients (77).

Prolactin (PRL) is a hormonal polypeptide produced in the pituitary glands and in extra pituitary sites – including immune cells – influencing both humoral and cell-mediated immunity. A metanalysis including a total of 10 studies evaluated PRL levels in BS patients and revealed similar prolactin levels compared to HCs, suggesting that it is unlikely that this hormone influences BS pathogenesis (78).

Adipokines are involved in the regulation of immune processes by upregulating the production of proinflammatory cytokines and by activating and promoting the differentiation of immune cells response. The potential role of these adipose tissue-produced peptides in BS pathogenesis is supported by a metanalysis (79) showing increased levels of leptin, resistin and adiponectin and lower levels of visfatin in BS patients compared to HCs.

Patients with BS reported stress/fatigue as the environmental factor most frequently associated to oral ulcers re-

currence (8, 48). In addition, Shenavandeh *et al.* (49) found that psychological stress circumstances such as nervous tension are a major trigger for oral ulcers, but not for other mucocutaneous nor ocular manifestations.

Discussion

The endogenous factors discussed such as age, ethnics and genetics, as well as exogenous factors such as diet, infections and smoking are related to the onset and clinical manifestations of BS. Some studies refer to epigenetic processes as a bridge between heredity, environment and disease, meaning that genetic factors induce individual susceptibility to disease, while epigenetics ultimately influence the occurrence and the development of the disease phenotype through environmental factors.

Among these epigenetic elements, DNA methylation influences and modulates several gene activities with catalysing DNA and using a set of DNA methyltransferases (DNMTs). As a matter of fact, many studies have confirmed that aberrant DNA methylation is involved in the pathogenesis of BS, and that DNA methylation status of many genes – e.g. cytoskeletal gene, HLA loci, Long interspersed nuclear element (LINE)-1, and Arthrobacter luteus (Alu) repetitive sequences – in BS patients is different from that of HCs. Also, miRNA polymorphisms and ubiquitination are thought to be involved in BS susceptibility and pathogenesis (80-83).

Therefore, via epigenetic mechanisms, the environmental factors modify the activation and/or deactivation of human genes and the disease status from the beginning. A better understanding of such epigenetic mechanisms may explain the environmental influence on BS, and will likely soon provide novel targets for treatment.

Conclusions

Infectious agents and microbiota are involved in the aetiopathogenesis of BS, although no specific agent has been isolated as clearly responsible for BS onset. Genetics and regional differences in disease expression make early diagnosis even more difficult for this complex and rare condition. Additionally,

other environmental factors such as diet, smoking and hormones may influence the clinical course of the disease and exacerbate some clinical manifestations. All those environmental factors carry out their effects through epigenetic mechanisms. A deeper understanding of the impact of these factors is necessary to improve therapeutic management and the prognosis of BS patients.

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