Asian Biomedicine Vol. 8 No. 2 April 2014; 139-155 DOI: 10.5372/1905-7415.0802.274

Review article

Behcet's disease: from heat shock proteins to infections

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Background: Behcet's disease (BD) is a chronic, inflammatory multisystemic condition of unknown etiology. Although the cause of BD is not clear, it is believed to be the result of an autoimmune process triggered by an infectious or environmental agent (possibly local to a geographic region) in a genetically predisposed individual.
Objective: To detail current knowledge of the role of microorganisms in the pathogenesis of BD and review the infectious etiology of this disease.
Methods: The review based on publication in SCOPUS, Science direct, and PubMed.
Results: A microbial infection has been implicated in the development of the disease to explain the strong inflammatory reactions observed, the activation of monocytes and macrophages, and the induction of proinflammatory cytokines and chemokines detected. Common factors linking some of the possible pathogenetic agents are extrinsically induced tissue stress or heat shock proteins, which react with host tissues and elicit significant T-helper type 1 cell responses.
Conclusion: Based on collected data, we conclude that the microorganisms discussed seem to participate and, at least in part, act as triggers during the course of BD. By clarifying the microbial associations of BD and finding its etiology, particularly the causative antigens leading to BD, it would be easier to suggest more effective treatment and preventive strategies for this disease.

Keywords: Bacterial infections, Behcet's disease, fungal infections, heat shock proteins, infectious etiology, microorganisms, viral infections

Behcet's disease (BD) owes its name to the Turkish physician professor Huluci Behcet, who, in 1937, described the classic trisymptom complex of hypopyon, iritis, and orogenital aphthosis [1, 145]. Today, BD is considered a more complicated entity [2] and is defined as a chronic, relapsing, multisystemic idiopathic inflammatory problem with mucocutaneous (erythema nodosum, pustular vasculitis), ocular (anterior and posterior uveitis), arthritic, vascular (both arterial and venous vasculitis), and central nervous system (meningoencephalitis) involvements [3-5]. The etiology and pathogenesis of this disease have been explored extensively [6]; genetic susceptibility, environmental factors (viral and/or bacterial infections), inflammatory response abnormalities (heat shock proteins (HSPs), dysregulated nitric oxide production) and abnormal immune responses play a major role in BD pathogeny [7]. Current evidence lends increasing support to immunoinflammatory mechanisms as one of the prime pathogenic processes involved in the development and progression of BD [8]. Common factors linking some of the possible pathogenetic agents are microbial stress or HSPs, which cross-react with host tissues and elicit significant immune responses [9]. The mean age at onset of disease is the third decade, children are rarely affected, and few neonatal cases have been reported [10]. This disease is prevalent worldwide, but a higher prevalence has been found among the Asian and Eurasian populations along the Silk Route stretching to the countries of the Mediterranean region including Turkey, Iran, Iraq, India, Korea, China, and Japan. BD has a higher prevalence in those countries (1:250 to 1:10,000) compared to USA and Europe (0.1–0.6:100,000) [5, 11].

The present review aims to detail current knowledge of the role of microorganisms in the pathogenesis of Behcet's disease and review the infectious etiology of this disease. A SCOPUS, Sciencedirect and PubMed review was conducted using the following keywords as search terms: "Behcet

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('s) disease and infection" and "Behcet ('s) syndrome and infection". The list of articles identified by this search strategy were examined and relevant studies were selected.

Etiology of BD

Although the cause of BD is unknown, it is believed to be result from an autoimmune process triggered by an infectious or environmental agent (possibly local to a geographic region) in a genetically predisposed individual [8]. Therefore, the possible etiological factors form a broad spectrum [genetic susceptibility, environmental factors (viral and/or bacterial infections), inflammatory response abnormalities (heat shock proteins, dysregulated nitric oxide production) and abnormal immune responses], with infectious agents being the most probable factors [7, 12].

Infectious causes

Infectious agents are believed to play a role in the pathogenesis of BD. Linked intrinsic and extrinsic factors are considered to contribute to the development of the disease, and this has led to the concept of environmental triggering of a genetically determined disorder [9]. An enhanced and dysregulated immune response has been suggested as the cause of BD manifestations, and environmental agents, including certain microorganisms, in genetically susceptible individuals, can trigger this [13]. For example, the "Behcet's Disease Research Committee of Japan" reported systemic BD symptoms one to two weeks after contact with *Streptococcus sanguinis, S. pyogenes, S. faecalis* and *S. salivarius, Escherichia coli* and *Klebsiella pneumoniae* [14]. Common factors linking some of the possible pathogenetic agents are extrinsically induced tissue stress or heat shock proteins, which react with host tissues and elicit significant T-helper type 1 (Th1) cell responses [15]. A microbial infection has been implicated in the development of the disease to explain the strong inflammatory reactions observed, the activation of monocytes and macrophages, and the induction of proinflammatory cytokines and chemokines detected [16]. BD is considered a chronic vasculitis, which is associated with infections. Infections have been associated with certain vasculitides and are presumed to be trigger factors of different types of vasculitis [17]. According to Kaneko et al. [18], immune responses based on a Th1 type reaction with chemotaxis to bacterial agents are considered to correlate with various BD symptoms, histologically exhibiting a "vascular reaction" or "lymphocytic vasculitis", or both. Infectious causes of BD and the role of microorganisms are reviewed in detail in next part of present review.

Immunologic causes

Both humoral and cell-mediated immunity are involved in pathogenesis of BD. Increased IgM and IgG levels in the serum of BD patients suggest a role for humoral immunity. Evidence of role of cell-mediated immunity include increase of $CD4^+$-T cells in the perivascular inflammatory exudates and increase in production of interleukin (IL)-2, interferon-γ and tumor necrosis factor (TNF)-α by T cells [19]. Elevated levels of IL-1β, IL-1RA, IL-2, interferon (IFN)-γ, IL-6, IL-8, IL-12, IL-15 (especially elevated in cerebrospinal fluid (CSF)), IL-18, TNF-α, soluble TNF-α receptor II, IFN-α, macrophage inhibitory protein-1a, and GM-CSF, suggest a hyperactivated inflammatory response in patients with BD [20].

Genetic factors

An association with human leukocyte antigen (HLA) B51 has been reported in certain parts of the world and in some familial clusters. The increased incidence in the Far East and in the eastern Mediterranean and association with HLA B51 suggest that genetic factors are important influences in the etiology of BD [21]. The role of HLA-B5 [15] has been studied extensively, but recent research showed that BD gene is located near the HLA-B51 gene, but not on this gene itself [22].

Environmental factors

Organophosphates, organochlorines, heavy metal intoxication, and allergens are environmental factors that may trigger initiation or exacerbation of BD [23].

Possible bacterial infections and BD

Streptococcus spp

As BD starts mostly from the oral mucosal surface (oral aphthae are the first manifestation in 70% of patients), oral microbial flora have long been implicated in the pathogenesis [4]. Oral health is impaired in BD and associated with disease severity (whether because of a direct role in disease pathogenesis or as a secondary effect of insufficient oral hygiene) [24-26]. Patients with BD generally have a high incidence of

chronic Streptococcal infections such as tonsillitis and dental caries in the oral cavity, and the hyperreactivity to Streptococcal antigens might be related to these chronic infection foci [27, 28]. Induction of severe symptoms of BD after dental treatment in two patients with stable BD, and a case report of recurrent neuro-BD after tooth extraction suggest a possible role of the *Streptococcus* spp in the pathogenesis of this disease [29, 30]. Moreover, dental and periodontal therapies can be associated with a flare-up of oral ulcers in the short term, but may decrease their number in longer follow-up [31]. Baharav et al. divided the animal models for BD according to the proposed etiological paradigm, and in their bacterial infectious models, four species of the *Streptococcus* genus (*S. salivarius*, *S. faecalis*, *S. pyogenes*, and *S. sanguinis*) were mentioned [32]. The frequency of isolation of *S. oralis* (uncommon serotypes of *S. sanguinis* KTH-1, KTH-2, KTH-3, and KTH-4) was higher in BD than in controls [33]. To analyze the immunopathologic mechanisms of BD, Yoshikawa et al. cloned and sequenced the gene (*bes-1*) encoding a Streptococcal antigen correlated with the disease, identified the protein produced by this clone using western immunoblotting, and found that Bes-1 seems to be homologous to the human intraocular peptide Brn-3b [34]. Later, this research group detected Bes-1 DNA (encoding a Streptococcal antigen) in samples of lesional tissues from patients with BD and patients with other inflammatory disorders who served as control subjects by performing polymerase chain reaction (PCR) analyses; thus, the presence of Bes-1 DNA seems to be closely related to the pathogenesis of BD and might elucidate the role of the Streptococcal antigen, Bes-1, in the BD lesions [35]. One study, demonstrated the neutrophil and lymphocyte reactions against *S. sanguinis* BD113-20 isolated from patients with BD, and showed that this strain had the capacity to stimulate activated neutrophils. This study suggested that both bacterial stimulation and host hypersensitivity are involved in the symptoms and pathogenesis of BD [36]. Yanagihori et al. examined interleukin 12 p40 (IL-12B) expression and production levels in response to *S. Sanguinis* antigen and found increased expression of IL-12 p40 mRNA and protein, in conjunction with IL-12 p70 induction, in peripheral blood mononuclear cells (PBMCs) from BD patients, which provides evidence for an antibacterial host response toward Th1-immunity mediated by IL-12 in patients with BD [37]. To evaluate the association of chronic Streptococci infection with clinical features of BD, Oh et al. investigated anti-streptolysin O titer (a Streptococcal antibody test widely used for the diagnosis of post-Streptococcal disease) compared with patients with recurrent aphthous ulcer showing a high titer of anti-streptolysin O in BD patients. Their results suggested higher incidence of tonsillitis and dental caries in BD patients supporting the theory of increased susceptibility to oral infection in BD patients [38]. Moreover, patients with BD have significantly higher antibody titers to *S. sanguinis* strains and the Streptococcal antigens by comparison with control groups [39, 40]. T cells from patients with BD are stimulated by Streptococcal antigens (RRE KTH-1 antigens) to produce IL6 [41]. *S. sanguinis* infection after heat or mechanical stress in germ-free mice can induce oral and ocular diseases similar to BD. Thus, it seems that the severity of oral tissue damage is important to trigger the disease [42]. In addition to *S. sanguinis*, *S. mutans*, *S. mitis*, and *S. salivarius* are observed in majority of patients with BD [5]. In the new diagnostic criteria for BD in 2003, Kaneko et al. included hypersensitivity skin reactions against Streptococci in the diagnosis as one of the references and the levels of disease severity of BD patients [18].

Staphylococcus aureus

In a study designed by Hatemi et al., the microbiology of pustular lesions in BD patients was explored in comparison with the pustules in acne vulgaris and they showed that pustules in Behcet's patients were infected and not sterile. According to their results, *Staphylococcus aureus*, and *Prevotella* spp were significantly more common in pustules from BD patients, while coagulase negative staphylococci were significantly less common [43]. There is a case report of aggravation of BD by gingivitis and carious teeth infected with methicillin-resistant *S. aureus*, which was dramatically improved after extraction of the carious teeth and administration of systemic vancomycin hydrochloride [44]. In another study, the relationship between nasal *S. aureus* carriage and BD was searched and not confirmed [45].

Borrelia burgdorferi

Onen et al. investigated the seroreactivity to *B. burgdorferi* antigens in patients with BD and compared it with that of healthy and disease controls; they found that the increased seroprevalence of

B. burgdorferi in the BD group was no different from that in control groups, so they suggested no association between BD and *B. burgdorferi* infection [46]. Nevertheless, in a study of uveitis patients including those with BD, increased seropositivity for *B. burgdorferi* was reported by enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA) compared with control subjects [47]. In a recent study, three different serological methods, namely IFA, ELISA and western blotting were employed to elucidate an association between BD and *B. burgdorferi* infection; but findings did not support a potential role for *B. burgdorferi* infection in the etiopathogenesis of BD [48]. There is also report of an unusual case of juvenile BD in a 12-year-old boy probably triggered by a tick bite or *Borrelia* infection, or both (although laboratory examination was negative for *B. burgdorferi*) [49].

Mycoplasma fermentans

Zouboulis et al. investigated the presence of antibodies against macrophage-activating lipopeptide (MALP)-404 from *Mycoplasma fermentans* in the sera of patients with malignant aphthosis, who fulfilled the criteria of the International Study Group for BD, and a possible correlation of *M. fermentans* infection with the disease in an ethics committee-approved case-controlled study [16]. This study showed that MALP-404 is responsible for macrophage activation and suggested the possibility that a *M. fermentans* infection in patients with malignant aphthosis predisposes these patients to a cross-reactive autoimmune response and precipitates the disease [16].

Mycobacterium tuberculosis

Iliopoulos et al. reported a case of primary tuberculous meningoencephalitis in a patient with known BD, whose CSF PCR study was positive for *M. tuberculosis*, as was the CSF culture. However, the patient had a suppressed cellular immunity because of cyclosporin A treatment and long-lasting corticosteroid therapy, which are predisposing factors for tuberculosis infection [50].

Helicobacter pylori

To determine the possible influence of eradication therapy on clinical features of BD, *H. pylori* IgG, IgM, and cytotoxin-associated gene-A IgG status in patients were analyzed compared with a control group; and slightly, but not significantly higher prevalence of *H. pylori* IgG seropositivity and significantly higher prevalence of cytotoxin associated gene A positivity in patients were reported. Eradication of *H. pylori* significantly decreased clinical manifestations such as oral and genital ulceration, arthritis/arthralgia, and cutaneous findings of BD, indicating that *H. pylori* may be involved in the pathogenesis of BD or disease activity might be enhanced as a result of induced inflammation or altered immunity [51]. In another study, a patient with the BD, resistant to treatment, demonstrated a proportional remission after *H. pylori* eradication treatment suggesting that anti-*H. pylori* antibiotherapy can reduce the development of new oral aphthous ulcers and, for a limited time, the frequency of recurrent attacks in patients with BD [52]. Avc et al. [53] found that although the *H. pylori* seroprevalence between patients with BD and controls was not significantly different, the number and size of oral and genital ulcers diminished significantly and various clinical manifestations regressed after the eradication of *H. pylori*. Moreover, endoscopic findings, eradication rate, and prevalence of *H. pylori* were shown similar in patients with BD and patients in the control group [54]. In another study [55], prevalence of *H. pylori* was not significantly different in BD patients compared with controls, but the authors believed that HSPs produced by this gastric pathogen might play a role in the pathogenesis of BD.

Moraxella spp

In one study, conjunctival flora in BD patients were compared with the normal population; significantly higher colonization of *S. aureus*, *Moraxella* spp, and *Streptococcus* spp were found in the conjunctival flora of BD patients compared with that of the control group; so the authors suggested bacterial etiology in the pathogenesis of BD [56].

Escherichia coli

Escherichia coli derived antigens enhanced the production of IFN-γ by T cells from patients with BD, suggesting that T cell hypersensitivity to several bacterial antigens may play a central role in the pathogenesis of this disease [41].

Chlamydia pneumoniae

A recent study has provided serological evidence of chronic *Chlamydia pneumoniae* infection in association with BD. *C. pneumoniae* is an intracellular

bacterium capable of causing chronic infections [57].

Heat shock proteins

HSPs are a group of evolutionarily conserved proteins that show high sequence homology between different species, from bacteria to humans [58]. Despite their evolutionary sequence conservation, even between microbes and their host self-homologues, these microbial proteins are highly immunogenic and have been implicated in the control of autoimmune inflammation because of a cross-reactive immune response [59]. In addition to their physiological roles, they are implicated in the pathogenesis of various immune-mediated disorders such as infections (tuberculosis, trachoma, lyme disease, syphilis, gastritis, candidiasis, malaria, histoplasmosis, Chagas' disease), auto-immune diseases (Behcet's disease, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, psoriasis, chronic gastritis, Hashimoto's thyroiditis), vascular thrombosis (atherosclerosis), and malignant disorders [60, 61]. The observation that eukaryotic and prokaryotic HSPs have high sequence homology promoted the hypothesis that HSPs might be potential candidates for molecular mimicry and could act as potentially dangerous autoantigens [59]. The hypothesis of molecular mimicry between microbial and self-HSPs in BD is supported by bioinformatics. The observed similarity supports the possibility that human HSP60 functions as a recruiting antigen and a response directed against microbial antigens might lead to the recognition of human HSP60 and other tissue-specific proteins containing similar epitopes [62].

HSP60/65 is an immunodominant antigen that is derived from mammalian/bacterial 60/65 kDa HSP. The increased expression of both self and infective stress proteins and the extensive sequence homology and cross-reactivity between microbial HSPs (better known as groEL) and human HSPs led to the concept that HSPs might be involved in the etiopathogenesis of BD [63-66]. In addition to the HSP60, other HSPs (such as αB-crystallin and HSP70) have been suggested to play a role in the pathogenesis of BD [12, 67-72].

Besides modulating inflammatory responses via the induction of HSP-reactive regulatory T cells, HSPs can directly activate the immune system through surface receptors such as toll-like receptor [59]. Toll-like receptors (TLRs) have been identified as a group of receptors that recognize specific patterns of microbial components, and regulate the activation of both innate and adaptive immune systems [73]. Toll-like receptors, which are expressed on phagocytes and other cells, recognize "pathogen-associated molecular patterns" in microbes and mediate inflammatory signal transduction [74]. Among ten different TLRs defined as members of human TLRs, TLR4 is the receptor most exhaustively investigated and has been shown to recognize and interact with HSP and lipopolysaccharide (LPS), which are regarded as antigens in BD [75]. Functional abnormalities of these receptors or different activation cascades by different microorganisms are associated with disease pathogenesis in BD [73]. Human HSP60 induces a potent inflammatory response in the innate immune system via its ligands, TLRs, and operates in a similar manner to that of classical pathogen-derived ligands and can thus activate nonspecifically the innate immune system and stimulates the maturation of dendritic cells [6]. In some studies, the expression of TLR1, TLR2, TLR4, and TLR6 on monocytes and granulocytes in patients with BD was investigated, which showed increased expression of TLR4, but not TLR2 and others, by peripheral blood mononuclear cells [73, 74]. Miura et al. [76] hypothesized that TLR4 polymorphisms may be associated with the risk of BD. Kirino et al. hypothesized that HSP60 stimulates not only antigen-specific autoimmune responses, but also the innate immune system through constitutively over-expressed TLR4 [73]. These data are consistent with the interpretation that the immune response against TLR4 ligands, such as HSP and LPS, plays an important part in development of BD [76]. By means of western blot analyses, the bacterial composition of the subgingival plaque and saliva collected from patients with BD was investigated and the levels of superantigen and HSP production by the oral bacteria isolated from these patients (groups of *S. salivarius* and *S. mitis* as predominant strains, *Prevotella* spp, *Fusobacterium* spp) was determined. The results indicated that the anaerobic strains isolated from the oral cavity of these patients produce HSPs and possibly that HSPs produced by microorganisms in the oral cavity might lead to the acceleration of oral membrane ulceration in patients with BD [76]. Besides their immunodominance as microbial antigens, under various circumstances HSP do elicit immune responses also when (over-)expressed as self antigens by cells or tissues. This seems to be a peculiar feature of HSP, especially because in many cases immune responses

to this self antigen are not associated with pathogenic autoimmunity [77].

Cellular immunity to HSP60/65

Increased T and B cell activity against 60/65 kDa HSP is observed in different ethnic populations in BD with both αβ and γδT cell responses [60]. HSP60 is a lymphocyte-activating agent that causes vigorous proliferation of T cells in an antigen-specific fashion [64, 78]. After uptake of HSP-peptide complexes by antigen-presenting cells and "cross-presentation" of HSP-chaperoned peptides on major histocompatibility complex class I molecules, a CD8-specific T-cell response is induced [9]. Self-HSP and/or microbial HSP homologous to the self-HSP activates self-reactive T cells specific to the HSP peptides. Bacterial HSP may activate self-HSP reactive T cells that have been rendered unresponsive by self tolerance mechanisms. This process would lead to positive selection of autoreactive T cells in BD [79].

T-cell epitope mapping has identified four peptides derived from the sequence of the 65 kDa HSP that stimulate specifically TCR-positive lymphocytes from patients with BD. These peptides (111–125, 154–172, 219–233, and 311–325) show significant homology with the corresponding peptides (136–150, 179–197, 244–258, and 336–351) derived from the human 60 kDa HSP. B-cell epitopes within mycobacterial HSP 65 or human HSP60 overlap with the T-cell epitopes and both IgG and IgA antibodies have been identified. Among the four immunodominant T- and B-cell epitopes, peptide 336–351 of the 60 kDa HSP is significantly associated with BD in the UK, Japan, and Turkey [80-87]. Furthermore, subcutaneous and mucosal administration of the peptide 336–351 of the human HSP60 induced uveitis resembling the eye involvement in BD in the rats [87]. In another study, oral p336–351 induced uveitis in rats was prevented by oral tolerization with the peptide linked to recombinant cholera toxin B subunit [88]. In general, the application of antigen through mucosal surfaces induces tolerance and not pathology [32]. Nagafuchi et al. found that the peripheral blood lymphocytes produced excessive IFN-γ and IL-12 in patients with BD, but IL-4 production in patients with BD was almost comparable to that in normal individuals [90]. High serum levels of IL-12 in parallel with an increased frequency of peripheral IL-2 and IFN-γ producing T cells support a strong, polarized Th1 immune response in vivo [91]. Saruhan-Direskeneli et al. characterized T cell lines in vitro for their epitope specificity to human HSP peptides to test the hypothesis of "molecular mimicry" in BD. The results demonstrate that the human proliferative response to mycobacterial HSP may also target the self-protein in both BD patients and controls. However, the responsive T cells may have different effects depending on their functional features such as cytokine secretions [62].

Antibodies against HSP60

Patients with BD have been shown to have antibodies against HSP60s, but the results of the ELISA antibody titer assays show that, although the various HSP60s share a common basic antigenicity, they differ in reactivity to the anti-HSP60 antibodies in the sera of the BD patients [64, 92]. Anti-HSPs are detected in inflammatory diseases, thus, antibodies to HSPs, regardless of Ig class (IgG, IgM, IgA), may be useful to detect inflammatory response of host cells [93].

Lehner et al. used a rabbit antiserum against a 65 kDa heat shock protein of *M. tuberculosis* and observed a 65 kDa band against six *S. sanguinis* strains examined and *S. pyogenes*; they also found raised IgA antibodies to the recombinant 65 kDa mycobacterial heat shock protein and to soluble protein extracts of *S. sanguinis* [85]. In another study, the antibody response against human HSP 336–351 and retinal ganglion cell peptides was determined. The number of IgG- or IgA-positive samples was significantly higher among patients with BD than in healthy controls, and the mean level of these antibodies in sera from BD patients was significantly higher than in controls [94]. An increased level of anti-HSP antibodies was found in the CSF of patients who had parenchymal neurological involvement [95]. By contrast, IgA antibodies specific for the HSP65 of *M. tuberculosis* could cross-react with certain serotypes of *S. sanguinis* [15]. Ramadan et al. [96], reported the presence of antibodies to HSP70 was determined in a number of endogenous uveitic conditions, and they concluded that raised levels of HSP70 antibodies are present in patients with purely ocular inflammatory disease such as pars planitis. Tanaka et al. found that the BD group showed significantly higher antibody titers than the control group in response to the HSP60 extracts from bovine retina extract (RetHSP), *Yersinia enterocolitica* (YerHSP), *S. pyogenes* (StrHSP), and retinoblastoma

cell line Y79 (Y79HSP), indicating that some unidentified autoantibody in the serum of BD patients recognizes HSPs. In this study, the response to StrHSP was significantly higher in the BD patients group than in the control group, strongly suggesting that this bacteria and particularly its HSP may play a role in BD [92]. Regardless of these data, Yurdakul and Yazici mentioned in their article that autoreactive T cells, the hallmark of true-to-form autoimmune diseases, seem not to be important in BD and the once-popular proposed role for increased T- and B-cell responses to heat shock proteins seems not to be of central importance [97].

Taken together, BD seems to result from heightened responsiveness to bacterial antigens in genetically susceptible hosts. In other words, Streptococcal HSP epitopes may reach the submucosa of the mouth ulcers and elicit an inflammatory reaction through upregulated HSP expression by minor injuries, which stimulate self HSP-60 reactive clones, suggesting different local HSP responsive T lymphocyte repertoire from that of peripheral blood. This, in turn, may serve as a local antigen with augmentation of inflammatory reaction [3].

Prophylaxis and treatment with antibiotics

Because exposure to Streptococcal antigens might be a major disease activity-provoking factor in BD and HSP65 is found in a variety of microorganisms, including *S. oralis* (uncommon serotypes of *S. sanguinis* KTH-1, KTH-2 and KTH-3), which has been frequently implicated as an etiological factor in BD, antibiotics may take a part in the prophylaxis and treatment of this disease. A randomized, prospective trial was conducted to evaluate the effectiveness of benzathine benzylpenicillin combined with colchicine in the prophylaxis of recurrent arthritis in BD patients. Significantly lower numbers of arthritis episodes and longer episode-free periods were observed in patients receiving colchicine plus benzathine benzylpenicillin for 24 months compared with patients receiving only colchicine, but the duration, severity, and pattern of arthritis episodes were found to be similar in both groups [5, 13, 80, 98]. Calg□neri et al. [99] concluded that prophylactic benzathine penicillin combined with colchicine is more effective in controlling mucocutaneous manifestations of BD than colchicine alone. Mucmu et al. evaluated the effects of azithromycin on mucocutaneous manifestations, oral health, and immune response in BD and showed that azithromycin was effective in decreasing folliculitic lesions and hastening the healing time of oral ulcers in BD [100]. Minocycline, an antibiotic to which certain strains of Streptococci are sensitive, reduced the frequency of clinical symptoms in BD patients as well as the production of proinflammatory cytokines by BD-PBMC stimulated with Streptococcal antigen [101]. Rozin reported a patient with refractory pustulosis of BD whose skin rash disappeared after a 6-week course of cotrimoxazole (sulfamethoxazole-trimethoprim), which is claimed to have antiinflammatory properties. According to this study, cotrimoxazole may be a promising treatment for controlling the microbial inductors and autoimmune reactions in BD [102].

Possible viral infections and BD

Herpes simplex virus

Baharav et al. divided the animal models for BD according to the proposed etiological paradigm, and in their review summarized the significance of herpes simplex virus (HSV) as a viral infectious model of BD [32]. By means of PCR, HSV has been detected in peripheral blood leucocytes, saliva, skin lesions, intestinal and genital ulcers of patients with BD [103-107]. However, other research groups could not detect the viral DNA in oral swabs collected from BD patients [108]. To test the hypothesis that HSV infection is one of the etiologic or triggering factors in BD, 258 ICR mice were inoculated with HSV type 1 (KOS strain); 29.8% showed Behcet's disease-like symptoms which were similar to the clinical manifestations of ulcers, uveitis, and arthritis [109]. In a study by Sohn et al., designed to determine the possible role of immune regulation in the development of BD-like symptoms, HSV-induced ICR mice were used successfully as animal models of BD [110]. There are also many other reports of using HSV-induced BD mice as animal models [111-118]. HSV-1 gene fragments in the peripheral blood mononuclear cells of BD patients were demonstrated by in situ DNA-RNA hybridization [119]. Other authors [120] reported a patient with the HLA-B51 haplotype with Behcet's disease-like symptoms concurrent with HSV-1 reactivation who fulfilled the Japanese classification for BD as incomplete BD; therefore, they speculated that the patient, who has an HLA-B51haplotype, could have an abnormal immunological response to HSV infection, resulting in the BD-like symptoms. The frequency of evaluable titers of anti-HSV-1 is greater in patients with BD (especially with ocular

involvement) than in the control series [121]. There is report of improving BD symptoms after administration of famciclovir (an antiviral compound that acts against HSV, varicella zoster virus and hepatitis B virus) from the day of lesion occurrence [122].

Human cytomegalovirus

Sun et al. found that the serum anti-human cytomegalovirus (HCMV) antibody concentrations in patients with recurrent aphthous ulcers (RAU) in the remission stage or BD were significantly higher than in control subjects and in patients with RAU in the active stage; providing evidence that HCMV may be a potential etiologic agent in some cases of RAU and BD [123]. Measuring the titers of IgG, IgM, and IgA anti-HCMV antibodies in 73 Korean patients with BD and comparing to scleroderma patients, systemic lupus erythematosus patients and healthy controls showed significantly lower antibody responses to HCMV in patients with BD. Meanwhile, the levels of anti-HSV-1 IgG antibody were assayed and found to be significantly increased in patients who had BD or scleroderma [124]. By contrast with previous studies, Sanchez Rom□n et al. [121] observed no differences in the distribution of titers vs. CMV compared to a control series.

Varicella zoster virus

The serological positivity for varicella zoster virus IgG and IgM antibodies in BD was not statistically different from other skin diseases [125].

Hepatitis viruses

To determine whether BD is associated with hepatitis viruses (hepatitis A virus: HAV, hepatitis B virus: HBV, hepatitis C virus: HCV, hepatitis E virus: HEV), serological markers of this four types of virus were studied in a BD group compared with healthy controls and a group of patients with systemic vasculitis. Results showed that seroprevalence of HAV, HCV, and HEV infections were not significantly different between BD patients and other groups of patients; however, previous HBV infection was found in a significantly lower number of BD patients [126]. According to Hadziyannis, most hepatitis C virus (HCV) infections are subclinical and in many of them nonhepatic rather than hepatic manifestations may prevail, such as skin disorders, including Adamantiades–Behcet's syndrome which may be linked to HCV [127]. To determine whether hepatitis B vaccination has any adverse effects on the course of BD, Erkek et al. conducted a study and observed no clinical sign of vaccine-associated exacerbation of disease activity, indicating that the activity of BD was not altered by HBV immunization [128]. Results of other studies demonstrate no association with hepatitis viral infections including hepatitis B, C, or G, with BD [129, 130].

Parvovirus B19

To investigate the possible role of B19 virus in BD, Kiraz et al. assessed antibodies against parvovirus B19 in serum samples from BD patients and found that their results did not strongly support the involvement of parvovirus B19 in the pathogenesis of BD. However, they believed that the presence of anti-B19 IgM antibodies in patients with BD might provide evidence for the place of B19 infection in the pathobiology of this disease [131]. By using quantitative PCR methods and immunofluorescence assays for IgG and IgM to B19, Baskan et al. found B19 DNA in the lesional skin samples of patients with BD and statistically significant rate of seropositivity for B19 IgG antibody. By contrast with previous reports, this study provides evidence for a possible causal link between BD and parvovirus B19 [132].

Epstein–Barr virus

Touge et al. assayed Epstein–Barr virus (EBV) antibody titers in patients' sera and reported an association between serological evidence of reactivation of EBV infection and uveitis in 19 patients with a mixture of sarcoidosis, BD and unclassified disease [133]. Sun et al. suggested that EBV might infect the epithelial cells of preulcerative oral aphthous lesions through EBV-infected lymphocytes. In addition, the cytotoxic T lymphocyte-induced lysis of the EBV-infected epithelial cells, but not the virus-induced cytolysis, may be the main mechanism causing oral ulcer formation. That provided preliminary evidence for an association of EBV with preulcerative oral aphthous lesions in BD patients [134]. Because interferons (INF) are natural defense mechanisms against viruses and inhibit their activities by enhancing major histocompatibility complex class I and cytokine expression, and viral infections such as Epstein–Barr virus and HSV may play a role in the pathogenesis of BD, the efficacy of INF-α-2b on mucocutaneous lesions of BD was evaluated and showed significantly

decreased numbers and sizes of oral, genital, and cutaneous lesions with less pain and longer duration of remission [135].

Human immunodeficiency virus (HIV)

Buskila et al. reported a case of BD developing in a young black woman with HIV infection and suggested that BD may be related to the HIV infection in this patient [136]. There has been report of anti-retroviral treatment of a patient with HIV infection who had developed BD in the absence of any HIV-related clinical disease; therefore the authors suggested the association of BD with HIV infection. However, the occurrence of BD and HIV infection may be coincidental; a Behcet's-like presentation of the complications of HIV disease, or HIV infection causing or predisposing to a Behcet's-like illness [137].

Possible fungal infections and BD

Candida spp

In a study designed by Hayasaka et al. the ratios of D-arabinitol (a major metabolite of *Candida* species) to creatinine were examined in patients with ocular inflammatory disease; and the ratios in patients with BD in the active phase were characteristically increased, suggesting the relation of *Candida* infection to the active phase of BD [138].

Saccharomyces cerevisiae

The presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) in patients with BD has been related to the pathogenesis of this disease. To evaluate the rate and clinical correlations of ASCA among healthy family members of patients with BD, Monselise et al. conducted a study and used healthy family members of patients with BD as a control group. They found that significantly higher mean IgG and IgA-ASCA levels in BD patients compared with healthy family members and healthy controls group; however, ASCA levels were also increased in healthy family members of BD patients, suggesting that they are probably influenced by genetic as well as environmental factors [139]. IgG and IgA ASCA levels in BD patients and in three control groups were measured by ELISA. Although the results of study demonstrated the significantly higher presence of ASCA in sera of patients with BD compared with other three control groups, but ASCA were not linked to a specific clinical manifestation of the disease and probably do not pose an increased risk for a more severe disease course [140]. Fresko et al. reassessed the level of IgG and IgA ASCA in 85 BD patients and found no significant difference between BD and group of diseased and healthy controls; however, there was a significant trend for patients with gastrointestinal (GI) involvement with BD to be more positive for ASCA compared with the rest of the patients with BD [141]. In another study, ASCA positive rate in BD, intestinal BD and healthy control subjects was shown to be 3.3%, 44.3%, and 8.8% respectively; however, clinical findings at diagnosis and cumulative relapse rates of intestinal BD were not found to be associated with ASCA expression [142]. There is also a report of a relatively high percentage of seropositivity for anti-*S. cerevisiae* Mannan antibody in patients with Crohn's disease and patients with BD compared with normal controls [143].

Possible parasitic infections and BD

Trichomonas vaginalis

There has been case report of a patient with a rectovaginal fistula and other manifestations fulfilling criteria for the diagnosis of BD, who had surgical closing of the fistula, but ten weeks after, regression of all symptoms of BD occurred, pointing to a probable relation between genitorectal *Trichomonas* invasion and this disease [144]. The author believed that primary genital and secondary rectal Trichomoniasis in patient caused maximal sensitization and mouth ulcers, and elsewhere was an allergic phenomenon. Direct cytopathogenic activity of parasites and their later toxic and allergic effects may play a part in the development of disease on mucous membranes, as well as on other tissues, which is found in BD [144].

Conclusion

Although the disease is not considered to be contagious, because no horizontal transmission has ever been reported [15], microbial pathogens have been postulated as either a causative agent or a disease-triggering factor in Behcet's disease (**Table 1**) [91]. There is considerable evidence that *S. sanguinis* and other Streptococcal antigens may have some etiological role in BD. Data on a possible association between other bacterial infections and BD are controversial. Thus, current data support the notion that BD may have a bacterial trigger, but how this trigger induces the disease is currently unknown.

Table 1. Infectious microorganisms and Behcet's disease

Infectious microorganisms	Supporting data
Bacteria	
Streptococcus spp	[4, 14, 18, 24-42]
Staphylococcus aureus	[43, 44]
Borrelia burgdorferi	[47, 48]
Helicobacter pylori	[51, 54]
Prevotella spp	[43]
Mycoplasma fermentans	[16]
Mycobacterium tuberculosis	[50]
Moraxella spp	[56]
Escherichia coli	[14, 41]
Chlamydia pneumoniae	[57]
Viruses	
Herpes simplex virus	[145, 32, 103-122]
Human cytomegalovirus	[123, 124]
Varicella zoster virus	[125]
Hepatitis viruses	controversial
Parvovirus B19	[132]
Epstein–Barr virus	[133-135]
Human immunodeficiency virus	[136, 137]
Fungi	
Candida spp	[138]
Saccharomyces cerevisiae	[139-142]
Parasites	
Trichomonas vaginalis	[144]

A viral etiology for BD was first postulated by Huluci Behcet in 1937 [145] and later several research groups implicated the possible role of a number of different viruses in BD [103-107, 113, 123, 146, 147]. Studies published to date support the role of HSV in pathogenesis of BD. Except for HSV; current evidence for viral etiologies is debatable. Etiological links between hepatitis viruses and BD seem unlikely, since a significantly elevated frequency of hepatitis A, B, C, E virus seropositivity has not been observed in patients with BD. The data suggest that Parvovirus B19, human cytomegalovirus, varicella zoster virus, EBV, and HIV are among a number of potential triggers in BD. There is a consensus that BD is not a result of direct viral infection by discussed viruses, but rather caused by a dysfunctional postinfection response.

Studies showing elevated HSP levels and anti-HSP antibodies, increased expression of HSPs and their receptors (TLRs), and cellular immunity to HSPs shed new light on the autoimmune nature of BD and the role of HSPs in this disease; a molecular mimicry between bacterial and self HSP may be associated with the development of the disease [80]. HSPs might trigger both innate and adaptive immune mechanisms in BD [18]. Recent clinical observations suggest that exposure to Streptococcal antigens (such as HSPs) may be a major factor for provoking disease activity [2]. By contrast, the therapeutic approaches involving HSP immunomodulation may be available as "oral toleration" [18, 89]. According to a recent study, a significant role of HSPs in BD immunopathogenesis through high sequence homology and molecular mimicry between microbial and self-8HSPs is suggested. When susceptible subjects to BD hold a bacterial infection, the bacterial HSP could be the trigger for an immune alteration. In these subjects, the high antibody levels to bacterial HSP could lead to a disease-specific cross-reactivity between mimicking epitopes (mimotopes), and the expressed human HSP could be a target to those autoantibodies [62].

Data regarding a possible association between fungal infection and BD are controversial and the role of ASCA as a marker for predisposition to develop future BD remains to be evaluated. Kotter et al. [148]

found that the manifestations of BD were similar in ethnically Germanic and ethnically Turkish individuals both living in the same German community, supporting the notion that environmental factors such as endemic infection may indeed be important in pathogenesis [149]. The role of infectious agents in the pathogenesis of BD would provide one explanation for why populations with similar genetic background living in different environments have different prevalence of disease [150].

Because BD patients are frequently on long-term immunosuppression that puts them at risk of infections, in addition to cases discussed here, there are reports of coincidental (opportunistic) infections (such as Nocardia spp) with BD or after receiving treatment for this disease. This condition has been related to treatment for this disease, usually consisting of a combination of systemic corticosteroids and an immunosuppressive drug like azathioprine or cyclosporine as first line approach [151-163].

A comparison of patients with BD in northern England and controls has suggested that the risk of the disease is related to oral ulceration in childhood, tonsillectomy, and cold sores requiring consultation with a doctor, and first sexual intercourse before 16 years of age. Risk was also related to larger families, later birth order, and travel to the Mediterranean littoral, Middle East, or Japan before the onset of symptoms. According to the authors, findings of this study are consistent with a triggering of BD in the UK by infection during childhood or adolescence in an immunogenetically susceptible host [164].

Based on these data, we conclude that microorganisms may trigger, potentiate, or participate in the pathophysiology of BD. Clarifying the microbial associations of BD may facilitate more effective treatment and preventive strategies for this disease.

Acknowledgments

This work was supported by a grant from the Research Council of Shiraz University of Medical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. The authors have no conflicts of interest to declare.

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