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Infectious Agents in Etiopathogenesis of Behçet’s Disease

Havva Ozge Keseroglu and Müzeyyen Gönül

Abstract
Behçet disease (BD) is a chronic, relapsing, multisystemic vasculitis with unknown etiopathogenesis. It is widely accepted that an altered immune response triggered by an infectious agent or by an otoantigen in a genetically predisposed individual plays major role in the pathogenesis of BD. In this chapter, the role of infectious agents in the etiopathogenesis of BD was discussed.

Keywords: Behçet’s disease, etiopathogenesis, infectious agent, streptococci, gut microbiota

1. Introduction
Behçet’s disease (BD) is a chronic, recurrent, inflammatory, multisystemic disease characterized by oral and genital ulcerations, uveitis, and skin lesions. Although the etiopathogenesis of BD is still unknown, it is thought that the altered immune response against some environmental triggering factors in genetically susceptible individuals plays a major role in pathogenesis. It is widely accepted that endothelial injury, neutrophils, and the tendency to thrombosis also contribute to the pathogenesis of BD [1, 2]. The presence of familial cases, unusual geographical distribution of the disease, and the strong association of BD with the major histocompatibility complex (MHC), suggests that genetic factors may play a role in etiopathogenesis [1]. But, genetic factors alone are not sufficient to elucidate the etiology of BD. Today, it is believed that the disease process is triggered by an unknown infectious or environmental agent in a genetically predisposed individual [3]. The studies showing a decrease in the risk for development of BD in people who migrate from the regions with higher prevalence for BD to the...
regions with lower prevalence support the role of environmental factors in etiology [4]. In this chapter, possible infectious triggering factors will be discussed.

Among the environmental factors, the role of infectious agents such as bacteria (Streptococcus, Helicobacter pylori, Mycoplasma fermentans, Mycobacteria and Borrelia burgdorferi) and viruses (Herpes simplex virus (HSV) type 1 and 2, hepatitis viruses, Cytomegalovirus, Varicella zoster virus (VZV), Epstein-Barr virus (EBV) and Parvovirus B19) is mostly emphasized [3, 5].

A decreased positive pathergy frequency after surgical cleaning of skin before pathergy testing, the reduction of the frequency and duration of mucocutaneous findings of BD with prophylactic penicillin treatment, and the greater frequency of chronic tonsillitis and tooth decay in these patients are important findings that suggest the role of microorganisms in BD [1, 5, 6].

Oropharyngeal pathogens are the most blamed agents in pathogenesis, as almost all individuals with BD have oral aphthae [7]. After dental procedures, increased frequency of oral ulcers and activation of disease support this view [5, 8]. It has been suggested that this condition occurs as a consequence of the passage of microorganismal antigens from oral cavity into the bloodstream [5].

2. Bacteria

Because of predominancy of streptococci in oral cavity and dental infections, they are the most frequently investigated bacteria in BD. In patients with BD, it has been shown that oral hygiene is impaired and periodontal scores are high associated with disease severity [9, 10]. The proportion of Streptococcus sanguinis in oral flora has been found to be higher in individuals with BD than in healthy individuals [3]. Antibodies against S. sanguinis and S. pyogenes have been detected more frequently in the sera of BD patients than in the control group [5, 8]. In one study, oral ulceration had occurred after application of streptococcal antigens to the oral mucosa by prick test [5]. It has been suggested that streptococci penetrate to the oral mucosa with their enzymes such as IgA 1 protease and neuraminidase and lead to the development of hypersensitivity against streptococci in BD individuals [5]. There are studies suggesting that, in addition to S. sanguinis there may be an association between S. pyogenes, Streptococcus faecalis, Streptococcus viridans, Streptococcus haemolyticus, and Streptococcus salivarius with BD [5, 8].

In addition to streptococcal antigens, it was shown that a common non-peptide antigen present in many bacteria, such as Escherichia coli, Staphylococcus aureus, can also activate γδ-T cells in BD. This finding suggests that T lymphocytes of BD patients are hyperreactive to bacterial antigens in general, not against a specific bacteria [3, 7, 11]. In one study, it was shown that T cells in BD patients are stimulated with staphylococcal enterotoxins even at low concentrations that could be achieved under physiological conditions and stimulate IFN-γ production much more than the control group. The increased sensitivity of patients T cells to the several bacterial antigens may explain the exacerbation of systemic symptoms of BD after infections, dental caries treatments, operations, or trauma [11].
H. pylori is another bacteria that have been investigated in relation to BD [12–14]. In some studies, the prevalence of H. pylori was found to be high in patients with BD, and it was suggested that there was a relationship between the presence of H. pylori and gastrointestinal involvement [12, 14]. Although improvement in symptoms of BD after H. pylori eradication treatment have been reported in some uncontrolled studies, there are studies that do not support this [5, 14].

There are reports that some other bacteria, such as M. fermentans, Mycobacteria, Prevotella, Fusobacterium and B. burgdorferi, also induce BD, but there is no strong correlation with them [3, 5].

3. Viruses

The possible etiological relationship between viral infections and BD has been first suggested by Hulusi Behçet, due to the observation of intracellular inclusion bodies in specimens taken from aphthous lesions and was investigated by many researchers [6]. The HSV-1 genome was detected in oral and genital ulcers of BD patients [3, 6]. The amount of HSV-1 DNA in leukocytes, blood and saliva samples, and the anti-HSV-1 antibodies in serum samples of BD patients were found to be significantly higher than control group [5, 6]. The presence of immunocomplexes containing HSV-1 antigen in the blood has also been reported [15]. Besides these studies supporting the role of HSV in etiology, the results of several other studies in which HSV DNA could not be demonstrated in leukocytes, oral, and genital ulcers of BD and, improvement in clinical symptoms could not be obtained with antiviral therapy against HSV virus, have lead to giving up the hypothesis that HSV plays a role in the development of BD [3, 5]. However, in the light of today’s information, it is thought that the immune response to HSV infection rather than active infection with HSV may play a role in the pathogenesis of the disease [5].

Since hepatitis viruses play a role in many vasculitic diseases, their role in the etiology of BH has been investigated. Although, in one study, Hepatitis B virus was detected more frequently in patients with BD, Hepatitis A, B, C, E and G viruses have not been shown to be associated with BD [5].

Parvovirus B19, considered to be the causative agent in the development of numerous vasculitic diseases, has been detected more frequently in non-ulcerous lesions of BD, such as erythema nodosum, papulopustular reactions, than genital and extragenital ulcers and control skin biopsies but these results are not enough to prove the role of parvoviruses in BD [5, 16].

In addition to these viruses, it has been suggested that there may also be a relationship between human immunodeficiency virus, VZV, Cytomegalovirus, EBV and BD, but this relationship has not been proved [5].

Although many infectious agents have been suggested in the etiopathogenesis of BD, there is no definitely proven or isolated microorganism that plays a role in etiology. For this reason, it is now widely accepted that BD does not originate directly from infectious agents, but microorganisms alter immune response leading to autoimmune and inflammatory diseases. So, the studies have shifted on the role of the heat shock proteins (HSP), the cytokine profile changes and, the T cell hypersensitivity.
4. Heat shock proteins

The more accepted view about the role of microorganisms in the etiology of BD is that the microorganisms mentioned in the etiology carry some antigens (HSP, etc.) which are similar to the human proteins and the resulting cross-reaction is the cause of the immunological response [4, 15, 17]. HSP is a group of proteins that are synthesized by all eukaryotic and prokaryotic cells, as a result of physiological shock (heat, anoxia, trauma, etc.) and microbial stimulus, and are expressed on the cell membrane [1, 3]. These proteins protect the cells from severe damage and premature death (apoptosis) [3]. Bacterial 65-kDa HSP (HSP65), which was isolated from mycobacterium at first, exhibits a largely similar amino acid sequence with human mitochondrial 60-kDa HSP (HSP60), and it is thought that the cross-reaction between them result in immune response [4, 17]. It is postulated that human HSP60-specific auto-reactive T cell clones are formed as a result of this cross-reaction and immunopathological changes of BD occur [8]. HSP60 can lead to production of proinflammatory cytokines (IL6, IL12, IL15, and TNF-a), expression of cell adhesion molecules (ICAM and VCAM) and Th1 immune response by binding to Toll-like receptors 2 and 4 [3].

5. Molecular similarity

Retinal S antigen present in the retina shows homology with HLA-B51 and HLA-B27. Immune-mediated response to retinal S antigen develops only due to retinal damage after uveitis [4]. These data suggest that Retinal S antigen may play a role in the pathogenesis of BD through molecular similarity [3].

Bes-1, a S. sanguinis gene, was found in the monocytes in mucocutaneous lesions of BD. The more than 60% similarity of the amino acid sequence of the Bes-1 gene with the human intra-ocular ganglion peptide, Brn-3b, suggests that the uveitis in BD may occur due to molecular similarity between the microbial and host antigens [18].

6. Antimicrobial peptides

Another research topic related to environmental factors is antimicrobial peptides. Çiçek et al. found serum and saliva concentration of hepcidin, an antimicrobial peptide, in patients with BD and recurrent aphthous stomatitis are lower than in the control group and concluded that low hepcidin levels may be associated with oral aphthous lesion development [19].

7. Mannose-binding lectins

Mannose-binding lectins (MBL), part of natural immunity, bind to mannose and N-acetylglucosaminomines on the surface of many microorganisms and lead killing of them by complement
activation [5]. It is thought that the low level of mannose-binding lectin detected in BD correlates with disease activity and is associated with the colonization of *S. aureus* in pustular lesions [20].

8. Gut microbiota

Recent data indicate that gut microbiota plays an important role in human health. The dysbiosis of gut microbiota has been implicated in the etiopathogenesis of many diseases. In a recent study, comparing gut microbiota of patients with BD and healthy controls, the genera Roseburia and Subdoligranulum were found to be significantly depleted in patients with BD. Also, the butyrate production was found to be significantly decreased in these patients [21].

9. Conclusion

The etiopathogenesis of BD is still unclear. Although many infectious agents have been proposed in the etiopathogenesis, there is no definitely proven or isolated microorganism that plays a role in etiology. Today, it is believed that the altered immune response against an unknown infectious triggering agent in genetically susceptible individuals may play a role in the pathogenesis of BD.

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