Behçet's disease : etiology and pathogenesis

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Behçet's disease is a chronic, multisystemic, relapsing inflammatory syndrome with mucocutaneous, ocular, cardiovascular, rheumatologic, neurologic, gastrointestinal, and pulmonary involvement. The etiology of the disease is unknown. However, many studies have been conducted regarding the etiology and pathogenesis of the disease. In this article, the literature about the etiopathogenesis of Behçet's disease is reviewed, and recent advances are emphasized. [Journal of Turgut Özal Medical Center 2(1):72-77,1995]

Key Words: *Behçet's disease, etiopathogenesis, vasculitis.*

Behçet hastalığı : etioloji ve patogenez

Behçet hastalığı mukokütanöz, oküler, kardiovasküler, romatolojik, nörolojik, gastrointestinal ve pulmoner tutulumla seyredebilen kronik, multisistemik, tekrarlayıcı inflamatuar bir sendromdur. Hastalığın etiolojisi bilinmemektedir. Bununla birlikte, hastalığın etiolojisi ve patogenezi ile ilgili birçok çalışma sürmektedir. Bu derlemede, Behçet hastalığının etiopatogenezi ile ilgili literatür gözden geçirilmiş, hastalığa ait son gelişmelerin belirtilmesi amaçlanmıştır. [Turgut Özal Tıp Merkezi Dergisi 2(1):72-77,1995]

Anahtar Kelimeler: *Behçet hastalığı, etiopatogenez, vaskülit.*

Behçet's disease (BD) is a chronic, multisystem disorder affecting mainly young adult males. The clinical triad of uveitis with oral and genital ulceration was probably first recognized by Hippocrates[1]. It was eventually named after Professor Hulusi Behçet, a Turkish dermatologist who, in 1937, recognized this syndrome as a separate clinical entity, probably caused by a virus[2]. Behçet's description of the findings promoted widespread interest, and the disease is termed either Behçet's disease or Behçet's syndrome.

BD is characterized by a relapsing inflammatory process of unknown etiology. The disease presents several clinical manifestations with mucocutaneous, ocular, intestinal, articular, vascular, urogenital and neurologic involvement. Confusion has arisen because of the disease's multisystem nature, which may draw the patient to various medical specialists.

EPIDEMIOLOGY

The true incidence of BD is largely unknown. It has a worldwide distribution with a clustering in the Mediterranean, Middle East and Far East. The estimated incidence is 1:10000 in Japan[3] and 5:100000 in Israel[1]. The prevalence rates of 10:10000 and 40:10000 have been suggested by two spot surveys of the adult populations in Turkey[5]. The incidence in the United States has been reported as 1:300000 people per year in Olmstead County, Minnesota[6], whereas in England it is 0.6:100000[1]. However, more recently, O'Duffy has reported a higher prevalence rate (1:20000) in Olmstead County, Minnesota. As it occurs most commonly between latitudes 30 and 45 north in Asian and European populations, an area which corresponds to the old Silk Route used for centuries by traders making the dangerous passage from the East to the West, BD has also been named as "Silk Route Disease"[8].

The disease occurs more often in men than women with a ratio of 2 to 5:1[9] but in England and the United States females may be affected more than males[1,7]. The mean age of onset is usually early in the third decade of life, although the disease may rarely appear in childhood or in the elderly[9]. Familial cases

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have been reported, implicating a genetic predisposition of the individuals who become affected by the disease[9] In children, although similar clinical findings observed in adults may occur, the frequency of ocular involvement is lower and unusual manifestations, such as myositis, appear to be more common[10].

ETIOLOGY AND PATHOGENESIS

The etiology of BD has not yet been established. Several studies on genetic, virologic, bacterial, immunologic and environmental factors have proposed evidence of different causative agents.

Genetics : BD has been shown to be associated with specific alleles of the human major histocompatibility complex (MHC), which supports the evidence of genetic factors involved in the pathogenesis of the disease. A strong association with the human lymphocyte antigen (HLA)-B5 and its split antigen HLA-B51, has been reported in patients with BD, particularly from Japan and Mediterranean countries[5,11] This relation appears to be weaker in the United Kingdom and United States[12]. The increase in certain HLA phenotypes shows an association with the different clinical forms of the disease, such as HLA-B5 appears to be related to the ocular form, whereas HLA-B27 and HLA-B12 have been reported when arthritic and mucocutaneous symptoms are prominent[13]. Mizuki et al.[11] have shown a significant increase of HLA-B51 and a significant decrease of HLA-DQw1 in the patients with BD, especially those with ocular lesions, suggesting that the relative changes of the HLA class II alleles (HLA-DR, -DQ, -DP) can be explained by a linkage disequilibrium between HLA-B and class II genes. Sun et al.[15] have also reported that although there is an increased trend of HLA-DRw6 and -DRw8 antigens in patients with BD, the difference in frequencies of HLA-DR and -DQ antigens is not significant compared to healthy controls. Thus, the susceptibility gene to BD is thought to reside around the HLA-B region rather than within the class II region[11].

Viral etiology : A viral etiology, particularly Herpes simplex virus (HSV), has long been postulated for BD. In early studies inclusion bodies have been found in scrapings from ulcers[3] suggesting the possible role of viruses in the pathogenesis. This evidence has been sustained by several studies. In a significant proportion of patients with BD, lymphocytes do not permit the replication of HSV-1

in cultures[14] and part of the HSV genome is transcribed in peripheral blood monocytes of patients with ocular and arthritic BD. On dot blot analysis of whole blood, an increased frequency of herpes simplex DNA has been detected, although it is not consistently present. Circulating immune complexes containing HSV antigens and anti-HSV antibody have been shown in BD[15-17]. In addition, immunoregulatory disturbances in the control of T-cell- mediated immune responses to HSV have been described in patients with BD. Other indirect evidence of a persistent viral infection in the pathogenesis of BD relates to increased lymphocyte chromosomal abnormalities[14] and the efficacy of acyclovir in the treatment of BD[18]. Denman et al.[19] have suggested that viruses such as HSV, act as promoters of abnormal lymphoproliferation in individuals with predisposing factors, possibly related to selective DNA repair defects, to induce several rheumatic diseases including BD. More recently, Studd et al.[16] have detected HSV-1 DNA in peripheral blood leukocytes of patients with BD, by using polymerase chain reaction. However, to date the absolute role of HSV in BD pathogenesis has not been completely defined.

Role of Streptococcus : There have been several reports suggesting the involvement of streptococci in the pathogenesis of BD. It has already been shown that patients with BD have a significantly higher incidence of history of tonsillitis and dental caries, probably due to streptococcal infection, and BD symptoms are induced by dental treatments[20]. The lymphocytes from patients with BD and recurrent aphthous stomatitis are sensitized by streptococcal antigens. Delayed skin reactions have been induced by Streptococcus sanguis, salivarius and faecalis antigens, and more interestingly systemic symptoms have been provoked by the injection of these antigens[21]. The proportion of S.sanguis in the oral flora of these patients is significantly increased as compared with controls and the buccal mucosa epithelial cells from patients with BD have been different in terms of S. sanguis adherence[22]. Also, serum antibody titers to S. sanguis strains have been significantly higher in patients with BD than those of the control group[20]. Lehner et al.[23] have reported an increase in antibodies to S. sanguis which are associated with heat shock or stress proteins. Therefore, in the pathogenesis of the disease, various microbial triggers including streptococci and HSV, might act by inducing a common antigen, such as heat shock protein[23]. Mizushima[24] has suggested that

immunogenetic predisposition and certain streptococci sensitize lymphocytes and produce polymorphonuclear (PMN) leukocyte-activating factors and, certain streptococci which have an immunologic cross reactivity to human tissue proteins, together cause the inflammation with hyperreactivity of PMN in BD.

Immunologic studies : Numerous immunologic abnormalities can be detected in patients with BD. The role of the humoral immunity in the pathogenesis of the disease has not been completely revealed. Several studies have demonstrated circulating autoantibodies against human mucous membranes[25,26], elevated IgG, IgM, IgA and alpha-2 globulin serum levels[27] with a low or normal levels of local secretory salivary Ig A[28,29]. Moderately raised levels of anticardiolipin antibodies (ACA), particularly Ig M isotype have been detected in BD[30]. Although several reports have noted normal B lymphocytes in the peripheral blood, decreased levels of B cells have also been reported[29,31,32]. Increased levels of circulating immune complexes have been shown in almost 50% of patients with BD which has a close association with the activity of the disease[33]. However the role of immune complexes is not clear.

Total hemolytic complement activity is also elevated, with a marked increase of C9 levels. C2, C3 and C4 levels are found to decrease before the uveitis attack. The deposition of C3 and C9 on the walls of blood vessels and the detection of C9 in the basement membrane of oral ulcer biopsy specimens have also been reported, which indicates the possible role of the activation of classical complement pathway in the pathogenesis of the disease[34,35].

Studies on total blood T-lymphocytes have yielded conflicting results. Normal, elevated or decreased values of T-lymphocytes have been reported[31,32,36]. A decrease in CD4+ cells (helper cells) and a concomitant increase in CD8 cells (cytotoxic/suppressor cells) with a decrease of CD4+/CD8+ ratio have been demonstrated, especially in patients with active disease[36-38]. More recently, Kahan et al.[38] have shown that, among CD4+ cells, the percentage of suppressor-inducer cells (a subpopulation of CD4+ cells which bears CD45RA antigens) is significantly lower in patients with BD, suggesting the defective suppressive function in these patients may be related to the decreased number of suppressor-inducer subpopulation and subsequently to the presence of inactive CD8+ suppressive cells. A decreased peripheral blood natural killer (NK) function has

been reported in patients with active BD which may be due to low serum level of interferon gamma and the presence of immature forms of NK cells[37-39]. However, in the inactive stage of the disease relatively high activity of NK cells has been observed, possibly caused by high levels of interferon gamma[39]. Suzuki et al.[40] have also demonstrated significant increases in circulating cytotoxic lymphocytes including peripheral blood NK cells.

Elevated serum IL-1 and IL-2 levels have been shown in BD. In addition, the failure of suppressor cells to respond to IL-2 has been demonstrated particularly in patients with early active disease and less prominently but consistently in patients with chronic active or inactive disease[11]. Increased and normal tumor necrosis factor (TNF) levels have been reported in BD[12,13]. Hirohata et al.[14] have demonstrated that T cells stimulated by bacterial antigens produce greater amounts of IL-6 and interferon gamma. Thus, they have postulated that T cell hypersensitivity to several bacterial antigens may play a central role in the pathogenesis of BD.

Coagulation and fibrinolytic activity : The basis of the thrombotic risk in BD is not understood. Hampton et al.[15] have been reported higher concentrations of plasma fibrinogen in Behçet's patients, which is in concordance with previous reports. In addition, higher levels of von Willebrand factor, tissue plasminogen activator inhibitory activity (tPA-1) and tissue plasminogen activator inhibitor (PAI-1) antigen have been detected. The latter two correlated with the disease activity. They have postulated that the abnormal fibrinolytic activity in BD is due to increased inhibition of tissue plasminogen activator.

Environmental factors : Since BD has predilections for certain geographic areas, investigators have focused on environmental factors to explain the pathogenesis of the disease. Administration of chemicals such as organophosphate, organochloride and particularly inorganic copper compounds could produce a mucocutaneogenital syndrome in animals mimicking BD. In several studies of patients with BD, blood and sural nerve levels of these compounds were elevated[16]. Shimizu et al.[17] have reported a significant correlation between increased levels of serum copper levels and the ocular attacks in BD, increase in the serum copper concentration preceded the ocular attacks and the higher the level of this trace element, the more severe the ocular manifestations. The increased levels of serum copper

may be due to the higher ceruloplasmin concentrations[16] observed in several inflammatory conditions including BD. Serum zinc levels[16,18] and selenium levels[16] have tended to be decreased in patients with BD. Selenium incorporates into the enzyme gluthathione peroxidase which protects body tissues against oxidative damage. As the deficiency of selenium causes a decrease in the activity of this enzyme, it may be speculated that the antioxidative mechanism is partially destroyed in BD[16]. Serum magnesium levels have been normal in BD[18].

Whatever the etiologic factor, the underlying pathogenesis of BD is vasculitis of small and large vessels leading to occlusion, local thrombus formation and disruption of the integrity of the vessel wall. The principle pathologic features are perivascular infiltrates of lymphomononuclear cells, papillary dermal edema and proliferation of endothelial cells leading to partial obliteration of small vessels and fibrinoid degeneration[19,50]. Proliferating cells possibly act as a nidus for thrombus formation[50]. The cell infiltrate is similar to that seen in delayed hypersensitivity[19]. Jorizzo et al.[51] have shown neutrophilic vascular reaction or leukocytoclastic vasculitis in the biopsy specimen obtained after intradermal histamine injection and suggested that mucocutaneous and possibly systemic lesions in BD result from immune complex-mediated vessel damage. Aydıntuğ et al.[50] have detected circulating autoantibodies directed against endothelial cells in patients with BD, particularly who have active disease, acute thrombotic events or retinal vasculitis. Although the exact pathogenesis of vascular injury in BD is unclear, it is likely that immunologic injury to endothelial cells plays a major role in the pathogenesis of BD.

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