

Approaching the Extrinsic Etiopathogenesis of Behçet's Disease: Can Microbes Prompt This Ailment?

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Abstract

This paper reviews analytically the possibility of active involvement of certain microbes in triggering Behçet's disease (BD). Among the blamed multifactorial etiopathogeneses is HLA-z51 allele with or without TNF and MICA alleles' involvement, geographical dimensions (30th and 45th degree latitudes in Asian and European populations), and some other microbes: *Streptococcus sanguis* and *herpes simplex virus*. To conclude, the structure of *streptococcus sanguis* and its analogous microbes may help perpetuate or fulminate the severity of BD. however, no known microbes can initiate it.

Keywords: Behçet's Disease; Etiopathogenesis; *Streptococcus Sanguis*

Introduction

Behçet's disease (BD) is a multisystem idiopathic vasculitis that demonstrates multi-systematic manifestations of which mucosal, ocular, gastrointestinal and vascular manifestations come atop. Since autoimmunity cannot fully explain BD, it is recently considered midway between auto inflammation and autoimmunity. Ironically, the serological test of anti-nuclear antibody (ANA) is usually negative. Autoantibodies, furthermore, do not play a significant role in aggravating the condition, nor do B cells [1].

To date, intrinsic etiology of BD are mostly leveled at a defective HLA-B51 allele with or without tumor necrosis factor and MHC class I chain related alleles [2] whereas extrinsic factors include local geographical influence [3], pertaining to the Silk Road: an ancient trading route between the Mediterranean and East Asia, and contagious microbial involvement. Again, all these controversial allegations are rebuttable by the unquestionable hitting of BD in genetically-free cases, outside the geoepidemiological territory. Recently, open-label clinical trials in Japan and Turkey have shown infliximab to be effective in ocular Behçet's disease [4]. Other treatment modalities combine steroids with colchicine, interferon (IFN)- α , cyclosporine, or azathioprine [5] or recruit Dapsone [6,7]. Azathioprine [8], interferon (IFN)- α [9] and three anti-TNF- α compounds, infliximab, adalimumab, and etanercept, have shown favorable results on preliminary tests [10,11]. Recently, Davatchi., *et al.* [12] concluded that rituximab is efficient in severe ocular manifestations of BD. Scanning theses therapeutic agents, there appears no mainstay treatment line. This reflects the inconclusive understanding of BD etiopathogenesis.

Behçet Disease and Microbial Pathogenesis

Streptococcus sanguis has been considered, for so long, a causative infectious agent in spreading BD. Moreover, a peculiar dysbiosis of the gut microbiota and a significant decrease of butyrate production were reported to be obvious in patients with BD in a study on 22 BD patients and 16 normal individuals [13].

Specific positive signals against streptococcal α -enolase were detected in 42.9% of BD cases, 14.3% of dermatomyositis cases, and 14.3% of Takayasu's arteritis patients [14]. This should highlight, on the one hand, the probability of shared pathways in the above mentioned occult rheumatic diseases. On the other hand, sharing sensitivity and specificity to streptococcal α -enolase with dermatomyositis and Takayasu's arteritis do stochastically question the fact of the streptococcal initiation of BD.

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Given the intrinsic hypersensitivity in skin and peripheral blood monocytes to exhibit a response to certain *streptococcus sanguis* antigens in BD patients, unlike healthy populations in the control group [15], *streptococcus sanguis* is purported to initiate, disseminate or, at least, exacerbate the severity of BD. Advocating molecular mimicry, both human *heat shock proteins* (HSPs), 60 kilodalton, and bacterial HSPs, cell membrane protein (65 kilodalton), activate gamma delta T-cells ($\gamma \delta$ T-cells) in BD patients, unlike the submitted cases in the control group[16]. However, HSPs are *ubiquitously expressed by stressed cells as well*. Interacting with immunopathologic leucocytes, at the mucosal surface in BD patients, was attributed to the inherent defect of HLA types. Nonetheless, the same ulcerative immunological reaction was reported in unaffected HLA [2]. That being the case, fathoming the etiopathogenesis of initiating BD requires painting or instigating new scenarios, other than this of *streptococcus sanguis* pathognomoncity.

Fundamental to tackle this point further is to consider three definitive circles. First, neutrophils are hyperactive in BD, with increased chemotaxis, phagocytosis, superoxide production and myeloperoxidase expression and produce several cytokines [17]. A comparable hyperactivity is pathologically conspicuous in some ethnic distributions: people of Arabic, Turkish, or non-Ashkenasi Jewish origin. All share a defected pathognomonic gene that is utterly concomitant with familial Mediterranean fever: MEFV. Familial Mediterranean fever runs in such races as an autosomal recessive disease in which neutrophils are, like BD, hyperactive [18]. Having tackled so, HLA involvement can be reassessed in the light of the striking predilection of the analogous two rheumatic diseases especially with introducing, using genome-wide association studies, new loci: L23R-IL12RB2, IL10, STAT4, CCR1-CCR3, KLRG4, ERAP1, TNFAIP3, and FUT2 [19]. Second, the oral cavity, where oral ulcers appear precociously, is a harsh environment where sheer forces are frequently applied: mastication forces. The teeth cusps can simply cause tear and laceration of the mucosal surface; enabling *streptococcus sanguis* and other microbes, which normally colonize the oral cavity and the GIT, to get accessibility toward overcoming the first defensive mechanism. Third, kissing and copulation induce neither hemorrhagic mucosal surfaces nor ulcers at the labial or vaginal mucosa. By the same token, cuddling and squeezing foster neither ecchymosis nor ulceration of the embraced cutaneous sites. Rationally, the applied pressure and contamination should have aggravated some manifestations if *streptococcus sanguis*, or any other microbiota, had been pathognomonic. Therefore, laceration or rupturing of the intact mucosal or cutaneous surface may seem essential to cause BD manifestations of pustules and ulcers.

In another vein, TNE, which is secreted by activated $\gamma \delta$ T-cells, in circulation and in mucosal lesions, and is expected to facilitate the aggravation of the disease, can be also secreted, along with other proinflammatory cytokines, by virally infected monocytes/macrophages [20] Given the vascular instability, permeability and dysregulation in BD patients, viral soluble glycoproteins should not be, therefore, excluded since many can cause an increased endothelial permeability and hemorrhage[21].

This brings to light the allegation of the viral etiopathogenicity of Parvovirus B19 [22], cytomegalovirus [23], and varicella zoster virus [24], which were claimed to take a crucial part in triggering BD. Moreover, Hulusi Behcet himself and others suggested the involvement of. Advocating this allegation, serum antibodies to HSV-1 and circulating immune complexes with HSV-1 were reported to be raised in BD patients. Notwithstanding, anti-HSV immunity is also common in normal subjects. Results about therapeutic effects of antiviral treatment in BD are, furthermore, scarce and controversial [25]. To summarize, the suspected microbial organisms are illustrated in figure 1.

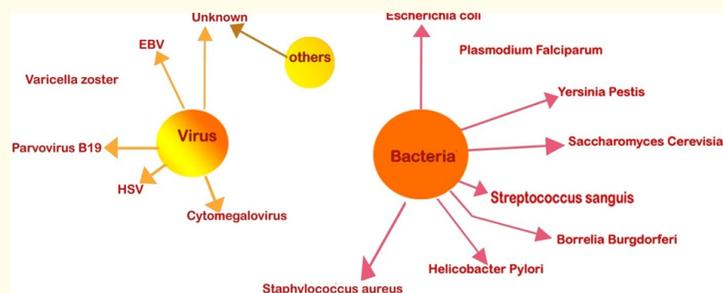


Figure 1: Diagram showing the suspected microbial organisms of BD initiation.

Conclusions

To conclude, the structure of streptococcus sanguis and other gut microbiota may help, through molecular mimicry, perpetuate or exacerbate the severity of the BD if surface integrity was compromised. Yet, no known microbes could have been proved to initiate BD. True to this claim is the involvement of ocular manifestations. Given the possible streptococcus sanguis to cardiac and endothelial vessels, this bacterium may help exacerbate the condition. Nonetheless, there appears no single clue as to the capability of this bacterium to trigger BD.

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