

Behçet's Disease as an Autoinflammatory Disorder

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Abstract: Autoinflammatory diseases are a group of heritable disorders that are characterized by seemingly unprovoked episodes of inflammation at certain locations and relative lack of high-titer autoantibodies or antigen-specific T cells. Behçet's disease is an inflammatory disorder of unknown aetiology, and many of its characteristic recurrent manifestations overlap with those of autoinflammatory diseases. Behçet's disease has a complex genetic aetiology, and it is more prevalent in certain geographic regions and/or in particular ethnic groups. Enhanced inflammatory response and over-expression of proinflammatory cytokines are the prominent features of Behçet's disease, and they are compatible with the findings in other autoinflammatory disorders. There are also evidences of antigen-driven immune response in Behçet's disease, but it possibly develops on the background of enhanced innate immune reactivity. Delineation of the similarities of Behçet's disease to other hereditary autoinflammatory diseases may help to clarify its pathogenesis and also to identify the missing links in the shared inflammatory pathways.

Keywords: Behçet's disease, autoinflammatory, familial Mediterranean fever, Crohn disease, inflammation.

INTRODUCTION

The recently emerged term of "autoinflammatory disease" is used to describe a group of heritable disorders that are characterized by seemingly unprovoked episodes of inflammation and relative lack of an obvious autoimmune pathology, i.e. pathogenic high-titer autoantibodies or antigen-specific T cells [1-4]. This group includes familial Mediterranean fever (FMF, MIM249100), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS, MIM260920), tumor necrosis factor receptor-associated periodic syndrome (TRAPS, MIM142680), Muckle-Wells syndrome (MWS, MIM191900), familial cold urticaria or familial cold autoinflammatory syndrome (FCAS, MIM120100), neonatal-onset multisystem inflammatory disease (NOMID, MIM607115), Blau syndrome (MIM186580), and pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome, or familial recurrent arthritis syndrome (PAPA, MIM604416) [3]. Most of these disorders are also known as periodic fever syndromes, because of recurrent episodes of fever along with self-limited inflammation at specific locations [4].

The recently discovered genetic bases of the autoinflammatory diseases have been linked to the mutations in genes encoding a relatively new family of proteins that have important roles in the regulation of apoptosis, inflammation, and cytokine processing. The genetic defects usually result in a continuous low-grade inflammatory activity; however recurrent inflammatory attacks at certain sites determine the clinical picture with a set of manifestations. In some cases, it may be difficult to make a differential diagnosis between them because of non-specific and overlapping clinical findings. Currently, the genetic defects alone do not help much to explain the predilection of inflammatory manifestations for certain sites in individual syndromes. However, involvement of different genes and their variable roles in the tissue-specific regulation of inflammation, background genetic effects, and environmental factors may contribute to the formation of different sets of clinical manifestations.

Although autoinflammatory diseases are relatively rare disorders, identification of their pathogenic mechanisms may enable us to understand the pathogenesis of more common inflammatory conditions. The link between two diseases characterized by granulomatous inflammation, the rare autosomal dominantly-inherited Blau syndrome and relatively more common Crohn disease, and their association with the variations in the CARD15 gene would be a good example in this context [5,6]. The CARD15 gene functions in the sensing of intracellular bacterial peptidoglycans through specific recognition of muramyl dipeptides and activates NF- κ B pathway [7]. The Blau syndrome is characterized by early-onset granulomatous arthritis, uveitis, skin rash and camptodactyly [5]. Three missense mutations were identified at the nucleotide binding domain (NBD) of CARD15 in patients with Blau syndrome, which were suggested to cause a 4-fold increase in the basal activity of the gene [5,7]. On the other hand, several sequence variations in the C-terminal leucine-rich repeats (LRR) domain of the CARD15 gene have been associated with an increased susceptibility to Crohn disease [5,7]. Crohn disease is

characterized by episodic intestinal and extraintestinal inflammatory manifestations along with granuloma formation, and has a complex genetic etiology. Crohn disease-predisposing LRR domain variants have been suggested to cause a defect in the recognition of colorectal luminal bacteria, which may result in a dysregulated inflammatory response [7].

Behçet's disease, an inflammatory disorder of unknown etiology, typically causes recurrent attacks at certain body sites, and it has been suggested to have a complex genetic background [8,9]. I herein discuss the similarities between the clinical and pathogenetic features of Behçet's disease and those of heritable autoinflammatory syndromes and propose Behçet's disease as an autoinflammatory disorder.

BEHCET'S DISEASE

Clinical Features

Behçet's disease is originally described as a triad of recurrent oral aphthous ulcers, genital ulcers and uveitis [10]. It is now recognized as a multi-system disorder manifesting with attacks of mucocutaneous lesions, arthritis, venous thrombosis, arterial aneurysms, intestinal ulcers, pulmonary lesions and central nervous system lesions [9]. Characteristic manifestations of Behçet's disease are recurrent, which may last a few days to several weeks, some of them leaving permanent tissue damage and causing chronic manifestations or even death. It usually starts in the third and fourth decades. The male to female ratio is near to equal in big series of patients, though Behçet's disease runs a more severe course in males and in those with a younger age of onset.

Mucocutaneous findings, including oral and genital ulcers, erythema nodosum-like vasculitic nodular lesions, acneiform lesions, papulopustular lesions and superficial thrombophlebitis, are the most frequently observed features of Behçet's disease. The skin pathergy reaction, another skin manifestation, has been recognized as a pathognomonic feature of Behçet's disease, and it demonstrates the hyperreactivity of skin to non-specific trauma [11]. It can be induced by pricking the forearm with a 20G hypodermic needle, and a positive reaction is defined by the development of an erythematous papulopustular skin reaction, similar to those observed spontaneously in patients, at the needle prick site at 48h [11]. A similar hyperreactivity can be elicited at other body sites, and other Behçet's disease manifestations such as oral and genital ulcers, arthritis, superficial thrombophlebitis and even arterial aneurysms can be induced following trauma [8,9,11].

The major causes of morbidity and mortality in Behçet's disease are due to the involvement of eyes, blood vessels, intestines and central nervous system [12]. Uveitis affecting both anterior and posterior tracts and retinal vasculitis can be seen in about half of the patients and recurrent attacks can result in a decrease in visual acuity or even a total loss of vision.

Vasculitis is an important feature of Behçet's disease and it characteristically affects both veins and arteries of all sizes with an accompanying thrombotic tendency [8,9,13]. Venous thrombosis can be seen in any vein with a thrombus sticky to the inflamed vessel wall. Arterial involvement is seen less frequently and can result in true and/or false aneurysms or less frequently a thrombotic occlusion. Endothelial dysfunction which results from immune-mediated inflammatory infiltrate is

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believed to be the basis of the observed vascular changes and thrombotic tendency in Behçet's disease [13].

Neurological manifestations include attacks of meningoencephalitis and parenchymal inflammatory changes mainly affecting the brainstem.

Aphthous ulcers can be seen in anywhere in the gastrointestinal tract, most frequently in the ileocaecal region, and can cause colicky pain, diarrhoea, bleeding and even perforation.

Arthritis attacks usually involve lower extremities, follow a monoarticular or oligoarticular pattern, and rarely run a chronic course.

Pathogenesis

The pathogenesis of Behçet's disease is unknown. An enhanced and dysregulated immune response has been suggested as the underlying pathology, and this can be triggered by environmental agents, mainly microbes, in genetically susceptible individuals [8,13].

Familial aggregation has long been noted in Behçet's disease, which gives a λ s value of 11.4-52.5 in Turkey [14]. Most of the multicase families did not show a particular Mendelian inheritance pattern. However, a classical segregation analysis provided an evidence for autosomal recessive inheritance in a paediatric subgroup [15].

Behçet's disease has been strongly associated with HLA-B51, and this association has been confirmed in different ethnic groups [9,13,16]. The direct role of HLA-B51 in the pathogenesis of Behçet's disease has long been debated. However, no other putative susceptibility gene in linkage disequilibrium with HLA-B51 has been identified yet. Allelic association, genotypic differentiation and stratification analyses in different ethnic groups have proved that HLA-B51 is showing the strongest association with Behçet's disease among all candidates in this region, which includes the tumour necrosis factor (TNF) and the MHC class I chain related gene-A (MICA) genes [17]. HLA-B*5101 heavy chain transgenic mice did not develop any of the Behçet's disease-related manifestations. However, these animals showed an increased neutrophil activity following f-Met-Leu-Phe (fMLP) stimulation compared to HLA-B35 and non-transgenic mice [18]. A similar enhanced neutrophil activity was also observed in HLA-B51 positive healthy individuals [18].

Genetic analysis of the multicase families suggested that the contribution of the HLA-B locus to the overall genetic susceptibility to Behçet's disease (λ_{HLA}) is less than 20% [19]. A novel susceptibility locus has been mapped to 6p22-23, and a whole genome screening of the multicase families has provided evidences for several non-MHC susceptibility loci for Behçet's disease [20,21].

The higher prevalence of Behçet's disease in a geographic area extending from the Mediterranean basin to Japan, between 30° and 45° latitudes North, may also have a genetic basis [22]. The frequency of HLA-B51 in the healthy population has been reported to be higher in this region. The geographic distribution also fits well to the ancient Silk Road, and it has been suggested that the genetic susceptibility to Behçet's disease might have spread via nomadic tribes, immigrating Turks or other traders along this route [16,22].

Enhanced inflammatory reaction is the hallmark of the pathological findings, which strongly suggest the activation of innate immune system. Spontaneous or induced over-expression of pro-inflammatory and Th1 type cytokines has been shown in various cellular sources, which may be responsible for the enhanced inflammatory response in Behçet's disease [9,13,23-24]. Neutrophil hyperactivity, characterized by increased chemotaxis, phagocytosis, superoxide generation and myeloperoxidase levels as well as a higher expression of CD11a, CD10 and CD14 on the cell surface, has also been suggested as one of the main pathogenic mechanisms in Behçet's disease [13]. Enhanced superoxide generation after fMLP stimulation suggests that neutrophils are primed *in vivo* in Behçet's disease, and increased production of interleukin-8 (IL-8), TNF and IL-1 from lymphomononuclear and/or endothelial cells might explain this primed state [13].

Some findings also support involvement of antigen-driven immune response in the pathogenesis, which is believed to be superimposed on the enhanced inflammatory reactivity [25-29]. Abnormalities have been observed in both $\alpha\beta$ and $\gamma\delta$ T cell subsets [13,25-29], and intracytoplasmic cytokine expression patterns and T-bet expression have indicated a strong Th1 polarization in Behçet's disease [30-32]. Oligoclonal T-cell expansions which correlate with clinical activity of the patients have supported the contribution of the antigen driven immune response to the pathogenesis of Behçet's disease [25]. These expansions can be induced by certain epitopes of the heat shock proteins (hsp) or other

antigens from different strains of streptococci or other microbial agents [13,26-29]. However, this increased responsiveness of T cells in Behçet's disease has not been confined to certain antigens, and it may reflect an intrinsic defect affecting signal transduction [26]. Some abnormalities have also been reported in both natural killer (NK) (CD16+CD56+) and CD56+ T cells, which may affect both innate and adaptive immune responses [13]. NK cells and/or other cytotoxic T cells can interact with class I HLA molecules through their killer immunoglobulin-like (KIR) and/or C-type lectin receptors. Engagement of these receptors has been shown to be associated with selective inhibition or activation of NK cell or T cell mediated cytotoxicity. The suggested pathogenic mechanisms for HLA-B51 molecule in Behçet's disease also include its interaction with KIR3DL1 or KIR3DS1 receptors on inflammatory cells [33].

SIMILARITIES IN CLINICAL FEATURES

Most of the Behçet's disease manifestations overlap with those of hereditary autoinflammatory syndromes (Table 1). Fever can also accompany some of the manifestations, and Behçet's disease has been listed among the disorders causing periodic fever syndromes [4,34].

Table 1. Manifestations of Behçet's Disease which Overlap with those of Autoinflammatory Disorders

Manifestations	Autoinflammatory disorders
Oral aphthous ulcers	HIDS
Genital ulcers	HIDS
Acneiform lesions	PAPA
Pathergy reaction	PAPA
Uveitis	Blau syndrome, NOMID, TRAPS
Arthritis	FMF, TRAPS, PAPA, Blau syndrome, MWS, HIDS
Meningoencephalitis	FMF, NOMID
Orchiepididymitis	FMF

HIDS: hyperimmunoglobulinemia D with periodic fever syndrome, PAPA: pyogenic arthritis, pyoderma gangrenosum and acne syndrome, or familial recurrent arthritis syndrome, NOMID: neonatal-onset multisystem inflammatory disease, FMF: familial Mediterranean fever, TRAPS: tumor necrosis factor receptor-associated fever syndrome, MWS: Muckle-Wells syndrome.

Recurrent skin lesions have been described in almost all of the autoinflammatory diseases: erysipeloid erythema in FMF, maculopapular rash in HIDS, acne and pyoderma gangrenosum in PAPA, urticaria-like rash in MWS, cold-induced urticaria-like lesions in FCAS, urticaria-like lesions, granulomatous, erythematous, papular rash in Blau syndrome and migratory rash overlying the area of myalgia in TRAPS [3]. However, the skin lesions of Behçet's disease are more similar to those of PAPA. Also, an association between the acneiform skin lesions and arthritis has been documented in Behçet's disease with a controlled study [35]. Interestingly, development of sterile abscess or ulcerative lesions at the injection sites has been described in patients with PAPA, which suggests a skin hyperreactivity quite similar to the pathergy reaction observed in Behçet's disease [36,37].

Both Behçet's disease and FMF are quite frequent in the Mediterranean basin and the Middle East, and they have many common clinical features. The shared clinical features may even lead to a wrong diagnosis in a patient of a Mediterranean background [38]. Co-existence of both conditions has been noticed by some investigators [39,40]. It is still a matter of debate whether the number of patients with concurrent Behçet's disease and FMF is higher than expected or not. However, sequence analysis of 8 patients with both Behçet's disease and FMF revealed that all patients were carrying only one mutation in the coding region of the MEFV gene [40]. The authors suggested that FMF may be expressed in individuals harboring only one MEFV mutation in patients with Behçet's disease [40]. Although FMF is an autosomal recessive disease, it is possible that it may be precipitated in individuals with a single mutation by factors depending on both the penetrance of the single MEFV mutation and the extent and nature of the other co-existent inflammatory condition. Hence, it is worth to rule out the possibility that one of the Behçet's disease susceptibility genes may be involved in the pyrin-related inflammatory pathways.

Similar to Behçet's disease, Crohn disease is also not a disease with a Mendelian inheritance pattern. However, it is the only complex disorder that has been documented to be associated with a gene linked to a hereditary autoinflammatory disease [6,7]. Many of the extra-intestinal manifestations of Crohn disease, such as oral and genital ulcers, erythema nodosum, uveitis and arthritis, overlap with those of Behçet's disease. In some cases, it is also difficult to distinguish the gastrointestinal involvement of Behçet's disease from that of Crohn disease [41,42]. We recently screened a group of Turkish patients with Behçet's disease for a possible association with the CARD15 gene, but no patient was identified as a carrier of three most common Crohn disease-predisposing CARD15 variants [43].

CONCLUSIONS

Behçet's disease is an inflammatory disorder of unknown aetiology, and many of its characteristic recurrent manifestations overlap with those of autoinflammatory diseases. In contrast to the hereditary autoinflammatory diseases, Behçet's disease has a complex genetic aetiology. However, epidemiological studies suggest that genetic factors have an important contribution to its pathogenesis, and similar to autoinflammatory disorders, Behçet's disease is more prevalent in certain geographic regions and/or in particular ethnic groups.

Co-existence of Behçet's disease in FMF patients with a single MEFV mutation may further support the definition of Behçet's disease as an autoinflammatory disorder, and they may share a similar inflammatory pathway. Enhanced inflammatory response and over-expression of proinflammatory cytokines are prominent features of Behçet's disease, which are compatible with the findings in other autoinflammatory disorders. There are also evidences of antigen-driven immune response in Behçet's disease, but it possibly develops on the background of enhanced innate immune reactivity. It has previously been suggested that Behçet's disease differs from a classical autoimmune disease with many of its features, which include the male dominance in severe disease, lack of association with other autoimmune diseases, lack of association with HLA alleles usually seen in autoimmune diseases, lack or paucity of autoantibodies and B cell hyperfunction-especially Sjogren's syndrome-and no definite T cell hypofunction, and the peculiar geographic and ethnic distribution [44].

Different autoinflammatory diseases are caused by defects in the regulatory pathways of inflammation/apoptosis that are closely related [45,46]. Delineation of the similarities of Behçet's disease to other hereditary autoinflammatory diseases may help to clarify its pathogenesis and also to identify the missing links in the shared inflammatory pathways. The further characterization of inflammatory features of Behçet's disease may eventually lead to development of better treatment options.

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