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Behçet's Disease: New Insights into Pathophysiology, Clinical Features and Treatment Options

Antonio Greco [1] M.D.; Armando De Virgilio [2] M.D.; Massimo Ralli [3] M.D. *; Andrea Ciofalo [1] M.D.; Patrizia Mancini [1] M.D.; Giuseppe Attanasio [1] M.D.; Marco de Vincentiis [1] M.D.; Alessandro Lambiase [1] M.D.

1. Department of Sense Organs, Sapienza University of Rome, Viale del Policlinico 155, 00100, Rome, Italy
2. Department of Otolaryngology-Head and Neck Surgery, Humanitas Clinical and Research Center, via Manzoni 56, 20089 Rozzano (MI), Italy
3. Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00100, Rome, Italy

Email addresses: antonio.greco@uniroma1.it; armando.devirgilio@gmail.com; massimo.ralli@uniroma1.it; andrea.ciofalo@uniroma1.it; p.mancini@uniroma1.it; giuseppe.attanasio@uniroma1.it; marco.devincentiis@uniroma1.it; alessandro.lambiase@uniroma1.it.

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*** Corresponding author**: Massimo Ralli, Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Viale del Policlinico 155, Rome 00186, Italy. Email: massimo.ralli@uniroma1.it

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Contents

1. Introduction

Behçet's Disease (BD) is a systemic inflammatory vasculitis of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions and other manifestations, including vascular, gastrointestinal, neurological involvement [1].

First description of BD, also known as the Old Silk Route disease, has been attributed to Hippocrates in the 5th century BC, in the "Third book of endemic diseases" [2, 3]. There are also descriptions of patients with constellation of symptoms and signs that are similar to BD since the 18th century all the way to the 20th century, namely by different authors [4-8].

In 1937, Behcet, a Turkish dermatologist, identified the 3 major signs (oral aphthae, genital ulcerations, recurrent uveitis) and grouped them on a clinical entity, publishing two reports [9, 10]. Before the II Word War he called this disease the "triple symptom complex" [11, 12].

However, six years prior to Behçet's description, Adamantiades, a Greek physician, is reported to have published an account of the disease in a French journal [13]. The disease complex became known as Adamantiades–Behcet's disease, although this term is rarely used today. The term "Behçet's Disease" should be preferred as suggested by International Society for Behçet's Disease [14].

2. Epidemiology

BD exists worldwide although there are significant regional differences, with the highest number of incidences in the Mediterranean, the Middle East, and the Far East [15]. The association of BD with the ancient trading route known as the "Silk Road" which extends from eastern Asia to the Mediterranean basin and the distribution of *HLA-B5* and its *HLA-B*51* subtype provides important clues to its origin. BD occurs most frequently between the latitudes 30º and 45º N in Eurasian populations (*Fig. 1*) [16-17].

The incidence of BD varies according to geographical location. Turkey demonstrates the highest

prevalence in the world, with up to 420 per 100,000 persons affected. Iran, Israel, northern China, and Korea follow with the next highest prevalence [18]. The countries with the lowest prevalence are the United Kingdom, Spain, Sweden, Portugal, and the United States, ranging from 0.3 to 6.4 per 100,000 persons [19, 20].

The onset of BD typically occurs in the third or fourth decade of life, and it is rarely seen in children or patients above the age of 50. The clinical courses of childhood-onset BD and late-onset BD are relatively benign. [17, 21-24].

BD shows a male preponderance in Middle Eastern countries and the Mediterranean; however, women are more commonly affected in Japan and Korea. [22, 25-27].

3. Etiopathogenesis

The cause of BD is unknown. It is believed to be due to an autoimmune process triggered by an infectious or environmental agent in a genetically predisposed individual [28, 29].

3.1 Genetic theory

The unusual geographic distribution of BD and pathology association with the allele of the major histocompatibility complex (MHC) locus, HLA-B51, may be the strongest indicator that certain genes are directly responsible for BD.

HLA-B51 allele located in the MHC locus, on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route, with a stronger association in Turkish and Japanese patients in comparison to Caucasians [16]. Studies have shown that *HLA-B*51* is associated with BD, with more than 60% of patients testing positive for *HLA-B*51* [30].

Other genes present in the MHC locus have been studied like HLA-B5701, associated with disease susceptibility and MICA (MHC class I related gene) and TNF genes, however, their participation is considered to be due to linkage disequilibrium with HLA-B51 gene [31].

Several other genes, located outside the MHC region have been proposed to be involved in BD pathogenesis. Meta-analyses identified that common variants of the *IL10* and encoding interleukin 23 receptor (*IL23R*)-encoding interleukin 12 receptor beta (*IL12B2*) genes were strongly associated with BD [32] IL23 is a proinflammatory cytokine that stimulates Th17 proliferation, increases the production of inflammatory cytokines, and increases the expression of IL-23 p19 mRNA in erythema nodosum-like skin lesions in patients with active BD [33]. IL10 is known as an anti-inflammatory cytokine that inhibits the action of proinflammatory cytokines, and the up-regulation of the CD4+ CD25+ T-regulatory cells in a BD-like mouse model improved the inflammatory symptoms via IL10 [34]. Therefore, the *IL10* and *IL23R-IL12B2* genes may play major roles in the pathogenesis of BD.

Factor V gene, also called factor V Leiden (FVL), have been associated with thrombosis and ocular involvement in BD with controversial results [35].

3.2 Infectious theory

Individuals from endemic areas who have immigrated to areas with low prevalence of the disease have an intermediate risk for developing the disease, which points that environment has some role in BD [1, 36]. Several microorganisms have long been postulated as possible environmental triggers of BD, specially Herpes simplex virus-1 and Streptococcus Sanguis [16, 37, 38].

The most commonly investigated microorganism in the pathogenesis of BD is Streptococcus. The relationship between streptococcal infections and BD is suggested by clinical observations such as a higher incidence of infections such as tonsillitis and dental caries, aggravation of BD and the beneficial effect of antibacterial treatments on mucocutaneous and arthritic symptoms [39].

HSV type 1 can be detected in saliva, intestinal ulcers, and genital ulcers by polymerase chain reaction in patients with BD compared with healthy controls [40, 41]. In addition, a BD-like mouse model was developed by inoculation of mouse earlobes with HSV and demonstrated HSV DNA sequences in cutaneous and gastrointestinal ulcerative lesions. Famciclovir seemed to be effective

in improving BD-like symptoms and preventing recurrence in a symptomatic mouse model [42]. However, to date, there is no information supporting the role of a single microorganism as the specific etiologic agent.

The most generally accepted theory for the role of infectious agents is that microorganism antigens have high homology with human proteins (like heat shock protein (HSP 65), obtained from Mycobacterium, which has high homology with human protein (HSP60) and that cross-reaction leads to immune response [38, 43].

3.3 Immunologic theory

Autoimmune reactions in BD are suggested to target primarily blood vessels, especially endothelial cells, causing the clinical presentation of vasculitis.

Anti-endothelial cell antibodies (AECA) have been described in many vasculitides, including BD and, in some of these diseases, their presence has been linked to the pathogenesis [44].

Lee, et al. [45] identified α-enolase as a target antigen of IgM-type anti-endothelial cell antibodies (AECA) in patients with BD using proteomic techniques. Several mechanisms were proposed in order to explain the action of AECAs in the pathophysiology of inflammatory diseases, including the binding of AECA to endothelial cells resulting in cell activation, which may in turn increase secretions of cytokines. AECAs might also trigger inflammatory processes by complement-dependent cytotoxicity and/or antibody-dependent cellular toxicity [18].

T cells are the major lymphocytes implicated in BD pathogenesis. T lymphocytes have an activated phenotype in BD and produce inflammatory cytokines [28, 46]

The discovery of new T cell subpopulations in the recent years has shed new light on BD pathogenesis. Numerous perturbations in T cell homeostasis have been reported. γδT cells and cytotoxic T cells, Th1 T cells, regulatory T cells (Tregs) and more recently Th17 cells have been implicated in the pathogenesis of BD [47].

γδ T lymphocytes play a major role in mucosal immunity as the first line of host defence. Evidence of an increased proportion of activated γδ T cells have been reported [48, 49] in BD and seems to play an important role in the pathogenesis of the disease. Culture of γδ T lymphocytes from BD patients proliferates in response to products from microorganisms in oral ulcers [50, 51]. Accumulation of γδ T cells in the sites of inflammation in BD has been reported [52].

Natural Killer T (NKT) cells are implicated in the control of autoimmune diseases. They can also regulate immune response through cytokine production or cell/cell contact. Activated NK cells have been reported to be increased in active BD patients [53, 54].

IL-8 is produced by T cells and is a major chemokine known to activate leukocytes, it was assumed to represent a link between immune system activation and endothelial alteration in BD. Elevated level of IL8 was reported in serum of BD patients, and in skin lesions and small vessel endothelial cell. IL8 was correlated with disease activity and vascular involvement [7, 55].

An increase in Th1 cytokine production has been found in peripheral blood of active BD patients and in lesions of active BD patients (ileal, mucocutaneous, skin) [56-58]. Th1 cells infiltrates including TNFα, INFγ, IL8 and IL12 was reported in oral and genital ulcer, and gastrointestinal lesions of BD [59, 60].

Geri et al. recently reported an increase of Th17 cells and a decrease of Tregs in peripheral blood of active BD patients.

IL21 is a recently identified cytokine produced by central memory activated CD4+ T cells also able to drive Th17 differentiation but also to modulate Th1 and Tregs cells [61].

IL21 and IL21 producing CD4+ T cells were dramatically increased in peripheral blood of BD patients and correlated positively with Th17 and negatively with Tregs, IL21 may act upstream of Th17 and Th1 pathways.

Th17, a subset of T helper cells, characterized by their production of IL17, has been more recently isolated and is implicated in many autoimmune/inflammatory disorders. IL17 promotes neutrophil-mediated inflammatory response [62]. Tregs have a central role in protecting an individual from

autoimmunity and have been widely studied in different autoimmune disorders [63, 64]. Activated Tregs were particularly decreased in BD patients. Tregs from BD patients were able to suppress effector cells meaning that they were functional [61].

Neutrophils are one of the major players of the innate immunity system. Neutrophil abnormalities have been extensively reported in BD. In vivo, the priming state of neutrophil has been reported among BD patients. The role of T cells in the neutrophil activation has been shown in experimental studies. High level of proinflammatory cytokines including IL8, INF γ and TNFα are suggested to be responsible for the prime state of neutrophils [28]. Strikingly, Th17 cells are implicated in the up-regulation of the neutrophil inflammatory response [65]. Neutrophil are directly implicated in specific lesions of BD as histopathological analysis of BD lesions showed venous and arterial infiltrates of neutrophils. It has been proposed to classify BD as a neutrophilic vasculitis [66] and the concept of the neutrophilic phlebitis was advocated [67].

Endothelial cells have pleiotropic functions which maintain the integrity of the vessel lumen to keep the blood flow intact. Many studies have reported endothelial dysfunction in BD. Endothelium is one of the main targets in BD, and endothelium dysfunction and activation have been clearly established [47].

Triggering factors such as viruses or bacteria are supposed to participate in the outbreak of BD. T cell homeostasis perturbation, especially Th1 and Th17 expansions and decrease regulation by Tregs are now supposed to be the cornerstone of BD pathogenesis. Inflammatory cytokine such as IL21 are playing a critical role in pathogenesis of BD. Inflammatory cells within BD inflammatory lesions included mostly neutrophils, and cytotoxic cells. Lastly, endothelium dysfunction and activation have been clearly established (*Fig. 2*).

4. Clinical manifestations

Despite being originally described as a dermatological disease, the major causes of morbidity and mortality result from ocular, major vascular and neurological involvement [68].

4.1 Mucocutaneous lesions

The mucocutaneous lesions constitute the hallmark of BD. Oral aphthae occur in 98% of cases and are mandatory in the international criteria of classification. Oral ulcers are a sine qua non feature of BD [69].

Painful oral ulcers appear in the tongue, pharynx, buccal and labial mucosal membranes. The typical lesion is round with a sharp, erythematous and elevated border, mostly 1 to 3 cm in diameter, but larger lesions can also occur.

Genital aphthae occur in 60 to 65% of cases and are very suggesting of the diagnosis of BD. They are localized in men on the scrotum and in women on the vulva and vagina where they can be disseminated and painful or totally indolent. They are morphologically similar to the oral ulcers but usually larger and deeper (*Fig. 3*) [70]. Other skin lesions are Erythema nodosum, Pseudofolliculitis, Papulopustular lesions, Acneiform nodules.

4.2 Eye manifestations

Eye involvement occurs in 30–70% of cases of BD and is cause of significant morbidity, about 25% of patients with ocular disease become blind despite treatment, although prognosis is improving with the use of modern immunosuppressant therapy. The typical ocular involvement is a chronic, relapsing bilateral non-granulomatous uveitis that may involve the anterior segment, the posterior segment or both (panuveitis) [14].

A variety of other eye lesions have been found including cataract, glaucoma, posterior segment involvement with vitritis, retinitis, and retinal detachment (*Fig. 4*).

4.3 Vascular manifestations

Vascular manifestations are characterized by involvement of vessels of all sizes, both in the arterial and venous systems and venous disease is more common than arterial involvement. Venous thrombosis occurs in 30% of cases. The arterial involvement is seen in 3 to 5% of cares [71]. The

incidence is probably underestimated because an autopsy survey showed that 33% of patients had arterial lesions, most of them had been asymptomatic [72, 73]. Cardiac involvement includes pericarditis, myocarditis, endocarditis [74, 75]. Aneurysms and/or thrombosis of the coronary arteries are observed complicated by hemorrhage, myocardial infarction and sudden death.

4.4 Articular manifestations

Arthralgia and/or arthritis occur in 45% of cases. They are frequently the presenting feature, long before the other manifestations. The knees and ankles are most involved, although smaller joints may also be affected [70].

4.5 Neurologic manifestations

They are observed in 20 to 40% of cases [76]. Central nervous system involvement in BD included parenchymal and non-parenchymal (i.e. cerebral venous thrombosis or arterial aneurism) lesions [77].

Parenchymal lesions (Neurobehcet's disease) frequently onset with an attack rather than a mild progressive course. They include headache, meningitis or meningoencephalitis, hemiplegia, or cranial nerve palsies [78]. Psychiatric symptoms including personality changes may develop.

4.6 Gastrointestinal manifestations

It is difficult to distinguish between BD and inflammatory diseases of the intestine, because of the similarity in intestinal and extra intestinal symptoms. This may explain the discrepancy of frequency ranging from 30% to 1% [79]. Gastrointestinal involvement causes nausea, abdominal pain, diarrhea which can be bloody and sometimes can lead to perforation. The ileocecal region is the most commonly affected part of the gastrointestinal tract, but tranverse colon and ascending colon are sometimes involved, as is the esophagus. Histologically, the intestinal ulcers are

indistinguishable from Crohn's disease, nevertheless the granuloma formation can be used to rule out BD.

4.7 Inner ear involvement

The otological features of BD can be divided into hearing loss and disequilibrium. Sudden sensorineural hearing loss was reported in two patients with BD [70, 80]

In the literature, there are many case reports about the inner ear involvement, and incidence of hearing loss in BD. In these studies, the incidence of HL has been reported as 12–80% [81-83].

5. Histopathology

The histology of the specific lesions shows vasculitis that differs from other forms of systemic vasculitis in that it involves both arteries and veins, and vessels of any size.

BD is a systemic vasculitis with significant neutrophil and mononuclear infiltration, endothelial cell swelling, and fibrinoid necrosis. Neutrophil infiltration is seen in all early lesions, including the skin pathergy reaction where minor trauma triggers a rapid cutaneous inflammatory response. In serum of patients with BD where found high levels of neutrophil priming cytokines such as TNF, interleukin 1b (IL-1b) and IL-8, as high myeloperoxidase levels generated by active neutrophils [1]. Mucocutaneous lesions show lymphocytic infiltration with immunoglobulin and complement deposition, and consequent liquefaction-degeneration at the junction between dermal and epidermal in association with necrosis and ending ulcer formation [1]. Mucocutaneous lesions may show leucocytoclastic vasculitis with IgM, IgG, C3 and fibrin deposits, consistent with an immune complex vasculitis [39].

6. Diagnosis

At least two ‘major’ signs of the disease should be present to make the diagnosis. These major signs include aphthous-like ulcerations of the oral mucosa, genital ulcerations, and uveitis [84] Other

systems reported to be involved through the course of the disease are inner ears with sudden cochlear hearing loss (HL), cardiovascular, pulmonary, gastrointestinal, central nervous system, skin and joints.

As there are no pathognomonic clinical or laboratorial findings of BD, several diagnostic criteria have been developed during the years, all having in common the 3 major features of oral ulceration, genital ulceration and eye lesions. In 1985 during the Fourth International Conference on BD, in London, an International Study Group (ISG) for BD was created, in order to create a set of criteria for the diagnosis of BD that could be used in the future. These ISG criteria were published in 1990, considering diagnosis of BD when recurrent oral ulcers plus 2 other features are present, in the absence of other clinical explanations (*Tab 1*) [69].

The pathergy test is the non-specific hyperreactivity of the skin following minor trauma and is a unique feature of BD [85]. It consists of the intradermal puncture of the skin with a 20-gauge or smaller needle 5 mm obliquely into the patient's flexor aspect of the avascular forearm skin under sterile conditions and without injecting saline. It is considered positive when an indurated erythematous small papule or pustule forms within 48 h. Positivity of the test varies with geographical location, being positive in more than 60% of Middle Eastern patients, in 15% of Korean patients and in about 5% of Caucasian, which considerably reduces its diagnostic values in populations with low positivity [31, 86]. A study demonstrated that surgical cleansing of the skin before the puncture reduced the test positivity [87].

Differential diagnosis plays a relevant role in BD. The diagnosis of BD is only supported by clinical criteria that require the exclusion of other diagnoses based on clinical presentation. Oral ulceration is not specific of BD as it may occur in 30-40% of the general population. In contrast, bipolar ulcerations are more specific of BD. Oral ulcerations may also be associated with hemopathy, HIV, Crohn's disease, lupus, bullous dermatosis or vitamin deficiencies. Sarcoidosis, Crohn's disease, Vogt-Koyanagi Harada [88] and Cogan syndrome [89] must be ruled out in case of ocular involvement. Venous involvement should exclude the antiphospholipid syndrome, or

thrombophilia. Arterial lesions of BD may mimic Takayasu's arteritis or polychondritis. Neuro-BD is sometimes difficult to distinguish from multiple sclerosis or Susac syndrome [90]. Lastly, chronic inflammatory bowel disorders must be ruled out in case of gastrointestinal involvement [70]. When audio-vestibular symptoms are present we must consider differential diagnosis with SSHL [91] and Meniere's disease [92].

7. Prognosis

BD has a variable course characterized by relapses and remissions. Prognosis depends on the clinical involvement. Loss of visual acuity and neurological disease are major causes of morbidity and disability. This rare disease, often leads to blindness and fatal systemic involvement [18].

Prognosis of BD improved in the last decade due to the use of modern immunosuppressant therapy and of a more aggressive treatment strategy [93, 94].

The mortality rate in adult cases varies with series, the highest was reported in Turkey (9.8%) and is related to large vessel vasculitis causing sudden-death by aneurysm rupture or thrombosis [95, 96]. Main causes of death include major vessel disease (43.9%) and central nervous system involvement (12.2%). The mortality rate at 1 and 5 years was of 1.2% and 3.3% respectively [70].

8. Therapy

Corticosteroids are commonly used to treat clinical manifestations of BD as a monotherapy or in combination with immunosuppressant drugs.

Corticosteroids can be used as topical therapy (ocular and mucocutaneous disease), and/or as systemic therapy (oral prednisolone (1 mg/kg/day) or intravenous methylprednisolone pulses (1 g/day for 3 days) [86]. When steroids are used, they can be reduced with caution after 4 weeks. Relapses are frequently seen after discontinuation of steroids.

Despite successfully decreasing acute inflammation, corticosteroids alone often fail to prevent relapses, so they are frequently used in combination with other medications. Combined treatment is also used in order to diminish corticosteroid dose [86].

Immunosuppressive drugs have been shown to be effective. Due to their delay of action, they are prescribed initially in association with corticosteroids. Azathioprine (2,5 mg/Kg/day) was proved effective in a controlled study [97]. Cyclophosphamide orally (2 mg/Kg/day) or intravenously (750 to 1g/m2 every 4 weeks) is also used. The efficacy of oral methotrexate (7.5 mg once a week) has also been reported. Cyclosporine A used in combination with corticosteroid has a corticosteroid-sparing effect, permitting the use of lower dosages [86]. Colchicine (1-2 mg/day has beneficial effects on the mucocutaneous symptoms [98].

Interferon α is a naturally occurring cytokine that has immunomodulatory properties. It has been shown to reduce the number of circulating γδ-T cells, and to inhibit T cell adhesion to endothelial cells in vitro [86, 99]. It was first used in the treatment of BD due to its antiviral activity against herpes simplex virus type 1 [100]. The doses of IFN-a used have ranged from 3 to 9 x10 alla 6 units 3 times a week; nevertheless, the optimum dosage and duration of interferon in the treatment of BD still needs to be determined.

Thalidomide has immunomodulatory properties, including diminished TNF production and activity and decreased neutrophil migration [101]. Thalidomide has reported efficacy in treating patients with mucocutaneous lesions refractory to treatment with colchicine. However, teratogenicity restricts usage of this drug [102, 103]. Contraceptive measures are mandatory due to severe foetal malformations.

We usually prescribe antiagregant therapy or anticoagulation in case of vascular involvement. Penicillin has been administered in Turkish BD patients as a prophylactic method to reduce the frequency and duration of mucocutaneous symptoms [104].

The recent progresses in the knowledge of BD pathogenesis pave the way for innovative therapy [105]. In contrast to current non-specific immunosuppressive agents mainly used empirically, the

emergence of biotherapies provides the possibility of interfering with specific pathogenic pathways. Novel targeted biotherapies might be used in the future for BD.

Meanwhile, the treatment of BD therapy remains still empirical, but nowadays new insights into BD immunopathogenesis have led to novel therapeutic approaches [106]. Clinical and laboratory observations suggested an important role of TNF-mediated process in the pathogenesis of BD [107, 108].

Tumor necrosis factor (TNF)-blocking agents such as Infliximab, Etanercept, and Adalimumab have been reported to have some success in patients with BD [107]. There is enough published experience to suggest that TNF blockade represents an important therapeutic advance for patients with severe disease who are resistant to standard immunosuppressive regimens and for those patients with contraindications or intolerance to these treatments [107].

Among the anti-tumor necrosis factor (anti-TNF) agents, Infliximab, an anti-TNFα chimeric monoclonal antibodies, has been used in more than 300 cases, mainly for refractory ocular BD and with 89% of improving patients who were resistant to conventional therapies [107-111].

Infliximab, was able to suppress in vivo and in vitro γδ T cells expansion, activation and cytotoxic activity [112]. This could be an explanation of the infliximab efficacy in BD and that underlined the important role of γδ T cells in BD pathogenesis.

The dosing regimen for Infliximab is 5mg/kg IV at weeks 0, 2, 6, and every 8 weeks thereafter [108, 113].

Etanercept is administered subcutaneously (SC) in a dose of 25 mg twice a week or 50 mg once a week. Etanercept was found successful in sustaining remission for mucocutaneous findings in significantly more patients than placebo [99, 114]. Adalimumab was administered SC as 40 mg every 15 days with god results [107].

9. Conclusions

BD is a systemic vasculitis, characterized initially by oral aphthous ulcers and then by systemic involvement. As there are no laboratorial findings of BD, the diagnosis is only supported by clinical criteria. Although the etiology of BD is still obscure the close correlation between the genetic internal and triggering external factors is thought to be present in the pathogenesis of BD.

T cell homeostasis perturbation, especially Th1 and Th17 expansions are now supposed to be the cornerstone of BD pathogenesis. IL21 may act upstream of Th17 and Th1 pathways and IL21 blockade represents a promising therapeutic target in BD. Further investigation is needed on the various aspects of the etiopathogenesis of BD.

The recent progress in the knowledge of BD pathogenesis may pave the way for innovative therapy. Recently it was reported a case of a patient with severe BD refractory to conventional therapy (corticosteroids and immunosuppressant) and infliximab that improved with Anakinra, a IL-1 blocker. This biological agent may be an option in the future for treatment of refractory patients. There is the need of further studies to determine efficacy of different therapeutic options in BD.

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Figure legends

Fig. 1. Global distribution of Behçet's disease. Dot size reflects prevalence. From: Cho SB, Cho S, Bang D. New insights in the clinical understanding of Behçet's disease. Yonsei Med J 2012;53:35-42

Fig. 2. Actual knowledge into Behçet's disease pathogenesis. From: Pineton de Chambrun M, Wechsler B, Geri G, Cacoub P, Saadoun D. New insights into the pathogenesis of Behçet's disease Autoimmunity Reviews 11 (2012) 687–698).

Fig. 3. a) Oral aphta and b) genital ulcerations. From: Kaneko F, Togashi A, Nomura E, Nakamura K. A new dignostic way for Behçet's disease: skin prick with self saliva. Genet Res Int 2014: 581468.

Fig. 4. Retinography and angiography images of central retinal vein occlusion on the right eye and branch retinal vein occlusion on the left eye. From: Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Gonçalves O, Valente J. Behçet's disease--a contemporary review. J Autoimmun. 2009 May-Jun;32(3-4):178-88.

Tables

Table 1: ISG criteria for the diagnosis of Behcet disease

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least 3 times over a 12-month period
Plus any 2 of the following:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in the vitreous on slit lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by the physician at 24-48 h

Abstract

Behçet's disease (BD) is a rare systemic vasculitis characterized by oral aphthous ulcers, genital ulcers, ocular lesions and other systemic manifestations. BD occurs most frequently in Eurasian populations along the ancient trading route known as the "Silk Road" which extends from eastern Asia to the Mediterranean basin. The causes of BD are unknown: it is believed to be due to an autoimmune process triggered by an infectious or environmental agent in a genetically predisposed individual. HLA-B51 allele located in the MHC locus, on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route. Herpes simplex virus-1 and Streptococcus have been postulated as possible environmental triggers of BD. T cell homeostasis perturbation, especially Th1 and Th17 expansions and decrease regulation by Tregs are now supposed to be the cornerstone of BD pathogenesis. The histology shows vasculitis that involves both arteries and veins, and vessels of any size. BD is a systemic vasculitis with significant neutrophil infiltration, endothelial cell swelling, and fibrinoid necrosis. The diagnosis of BD is only supported by clinical criteria and require the exclusion of other diagnoses based on clinical presentation. There are no pathognomonic laboratorial findings of BD. This rare disease often leads to blindness and fatal systemic involvement. Main causes of death include major vessel disease and central nervous system involvement (Neuro-Behcet). Corticosteroids are commonly used to treat clinical manifestations of BD in combination with immunosuppressant drugs. Tumor necrosis factor (TNF)-blocking agents such as Infliximab, Etanercept, and Adalimumab have been reported to have success in patients with BD.

Keywords: Behçet's disease, vasculitis, autoimmunity, immunology, oral aphthae, genital aphthae, uveitis, anti-endothelial cell antibodies.

Highlights

- Behçet's disease is a systemic vasculitis characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, ocular lesions and other systemic manifestations. Vasculitis involves both arteries and veins, and vessels of any size.
- The causes of Behçet's disease are unknown. It is believed to be due to an autoimmune process triggered by an infectious agent in a genetically predisposed individual. HLA-B51 allele has been the most strongly associated risk factor for Behçet's disease. Triggering factors such as viruses or bacteria are supposed to participate in the outbreak of Behçet's disease. T cell homeostasis perturbation is now supposed to be the cornerstone of Behçet's disease pathogenesis.
- The diagnosis of Behçet's disease is only supported by clinical criteria. The pathergy test is a unique feature of Behçet disease but has a limited diagnostic value. There are no pathognomonic laboratorial findings.
- Corticosteroids are commonly used in combination with immunosuppressant drugs. Tumor necrosis factor (TNF)-blocking agents such as Infliximab, Etanercept, and Adalimumab have been reported to have success in patients with Behçet's disease

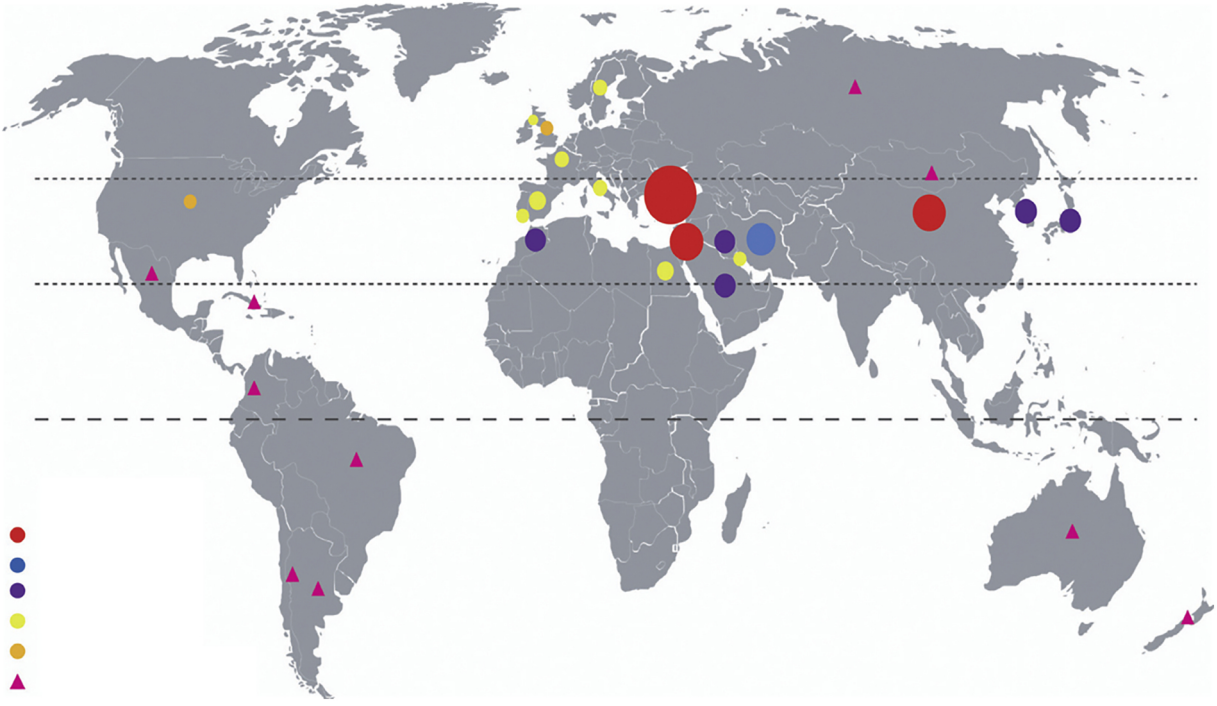


Figure 1

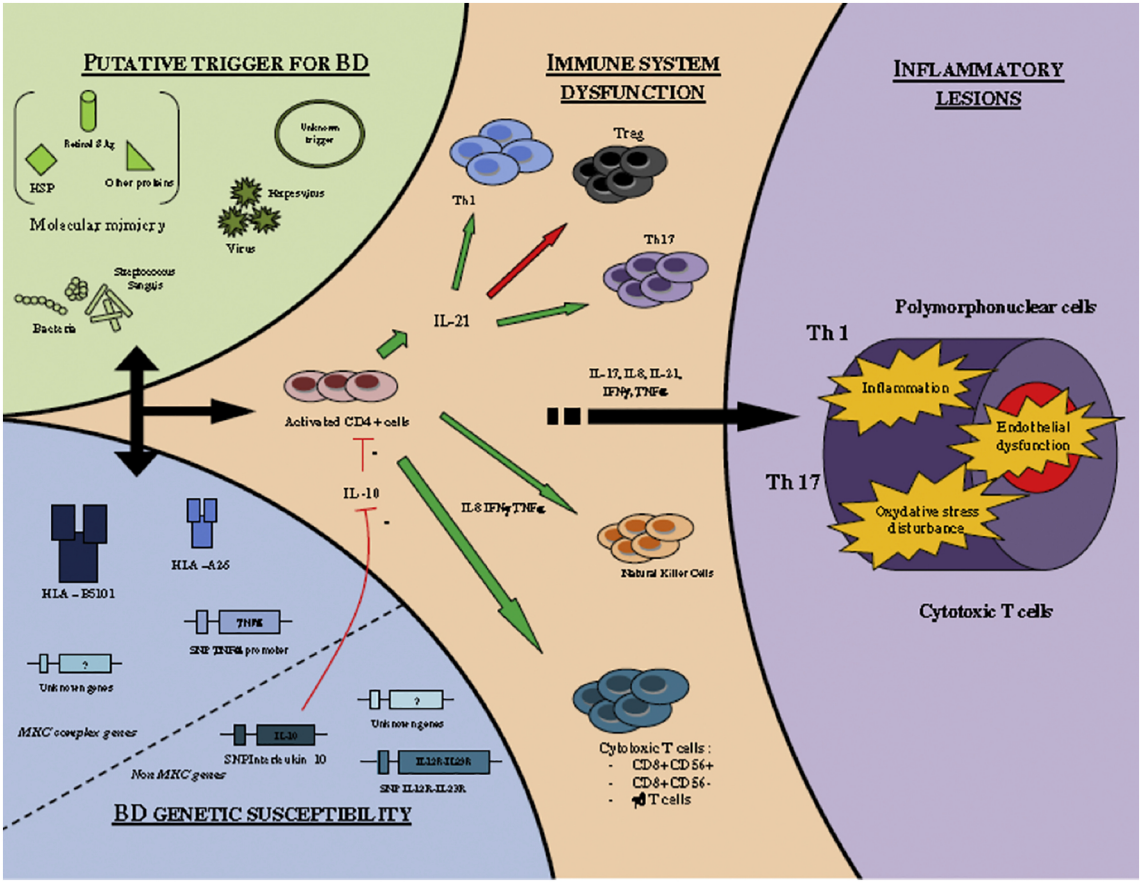
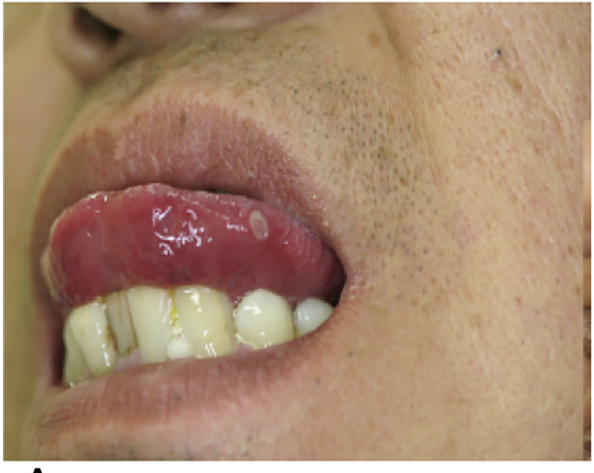
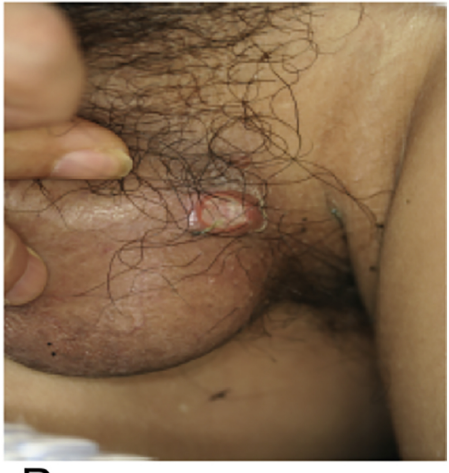

PUTATIVE TRIGGER FOR BD
Retinol BAg
HSP
Other proteins
Molecular mimicry
Unknown trigger
Herpesvirus
Virus
Streptococcus Sanguis
Bacteria
IMMUNE SYSTEM DYSFUNCTION
Th1
Treg
Th17
IL-21
Activated CD4+ cells
IL-10
IL-17, IL-8, IL-21, IFNγ, TNFα
IL-8 IFNγ TNFα
Natural Killer Cells
Cytotoxic T cells :
- CD8+CD56+
- CD8+CD56-
- γδ T cells
INFLAMMATORY LESIONS
Polymorphonuclear cells
Th 1
Inflammation
Endothelial dysfunction
Th 17
Oxydative stress disturbance
Cytotoxic T cells
HLA – B5101
HLA –A26
TNFA
SNP TNFα promoter
?
Unknown genes
MHC complex genes
IL-10
SNP Interleukin 10
Non MHC genes
?
Unknown genes
IL12R-IL23R
SNP IL12R-IL23R
BD GENETIC SUSCEPTIBILITY

Figure 2



A



B

Figure 3

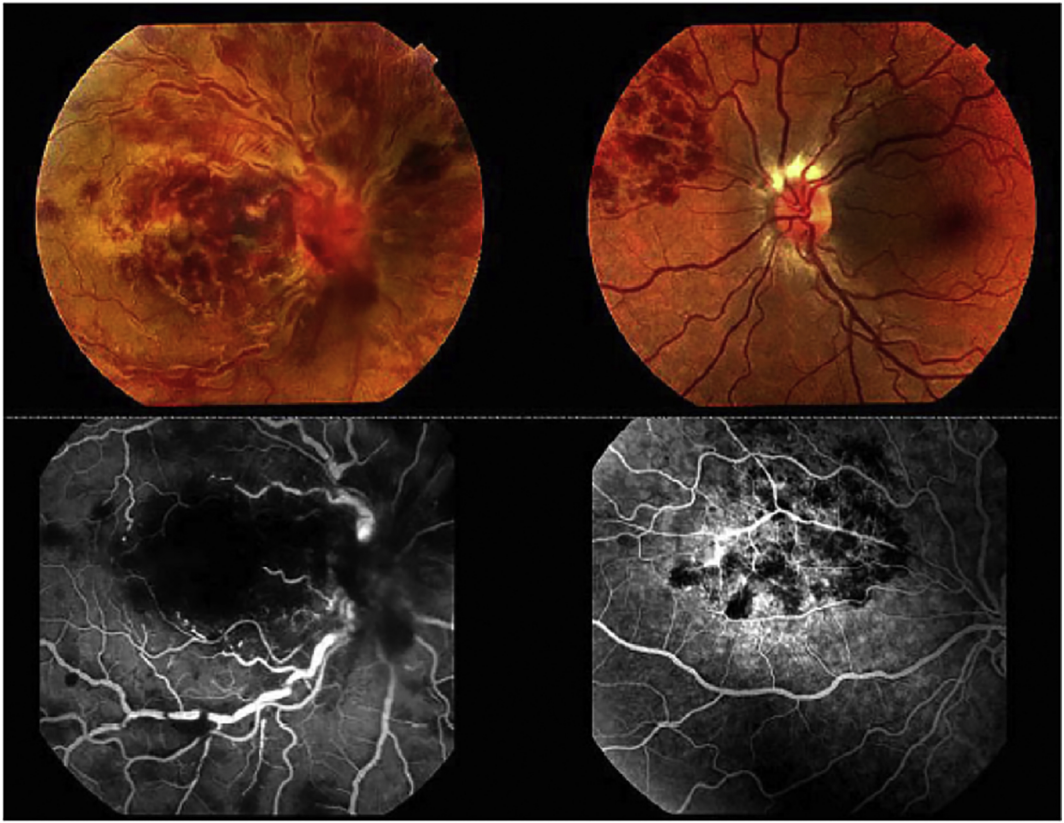


Figure 4