International Journal of Research in Medical Sciences
Reyes-Weaver DA et al. Int J Res Med Sci. 2022 Jan;10(1):279-284
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20214828

Review Article

Behcet's disease: a review

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Received: 21 November 2021
Revised: 06 December 2021
Accepted: 07 December 2021

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ABSTRACT

Behcet's disease (BD) is a complex systemic vasculitis with an etiopathogenesis that remains unclear. It has a strong geographic association as well as a genetic propensity linked to the HLA-B51 factor and interactions between genetic and environmental factors. The typical age of onset is 25 to 40 years old and it is more common in men, who also have a more severe condition. Occlusive vasculitis is the hallmark of this condition, which can affect vessels of all diameters. Oral ulcers, genital ulcers, skin lesions, pathergy reaction as well as involvement of other systems and organs such as ophthalmic, neurological and vascular lesions, among others, are used to make the diagnosis. Uncontrolled neutrophil activation, activation of the humoral and cell immune systems, toxic proteins and infectious agents such as herpes simplex and streptococci are all involved in their pathophysiology. Due to the heterogeneity and several systems affected, the treatment is individualized and focused on treating each clinical manifestation.

Keywords: Behcet disease pathophysiology, Behcet treatment, Vasculitis

INTRODUCTION

Hippocrates initially defined BD, also known as Behcet's syndrome, in the "Third Book of Endemic Diseases" in the 5th century BC.[1,2] Hulusi Behçet, a Turkish dermatologist, first described it in 1937 as a triple combination of symptoms that included mouth ulcers, genital ulcers and anterior uveitis with hypopyon.[3] Other clinical symptoms have been identified as part of this disease over time.

BD is an uncommon multisystemic vasculitis that affects the skin, joints, eyes, mucous membranes, gastrointestinal, musculoskeletal, cardiovascular and neurological systems as well as any kind and size of blood vessel.[4] It is a chronic, relapsing-remitting disease with a high morbidity rate that is typically recognized late due to the wide range of symptoms, the necessity to rule out other diagnosis and the lack of clear disease indicators.

Epidemiology

Because of its ties to the old trade route that went from East Asia to the Mediterranean basin, it's also known as silk road illness. The Mediterranean, the Middle East and the Far East are the most affected. In Eurasian populations, BD is most common between 30° and 45° north latitude.[4,7] Turkey has the highest prevalence, with up to 420 cases per 100,000 people; Israel, Iran, Korea and Northern China follow.[7] As of 1 January 2000, the age and sex-adjusted prevalence of BD in the United States was 5.2 per 100,000 people. Women had a larger incidence than men (0.51 versus 0.26, respectively). Men's incidence was higher in their fifth decade of life, while women's incidence was higher in their third decade.[8] Although few cases have been documented in Mexico, the precise number of cases remained unknown.[9]

The disease normally appeared in the third to fourth decade of life, with the exception of children and people

over the age of 50, who have a more benign outcome.[4-6] In Mexico, the majority of individuals developed the condition between the ages of 18 and 32, with a 5:1 ratio of women to men.[9] Men have historically been more commonly affected in the Middle East and Mediterranean countries; however, women were more frequently affected in Japan, Korea, Spain, Portugal, the United Kingdom, Israel, Sweden, Brazil, the United States and Mexico.[2,7-9]

Diagnosis

The diagnosis of BD is clinical; however, because of the various and intermittent symptoms, the necessity to rule out other illnesses and the lack of precise disease signs, the diagnosis is sometimes delayed. Three classifications were used to determine criteria for diagnosis.

International study group criteria 1990 (ISG): recurrent oral ulcers (at least three times in one year) plus two of the following genital ulcers, eye lesions, skin lesions and/or pathergy test.[10]

International criteria for BD 2006 (ICBD): recurrent oral ulcers as mandatory criteria, recurrent genital ulcers (2 points), ocular lesions (1 point), skin lesions (2 points), positive pathergy test (1 point) and vascular lesions (1 point). Diagnosis was made with the mandatory criteria plus 3 points.[11]

International criteria for BD (ICBD) 2014: oral ulcers (2 points), genital ulcers (2 points), ocular lesions (2 points), dermal lesions (1 point), vascular lesions (1 point) and neurological lesions (1 point), optional positive pathergy test (1 point). The pathergy test was optional and it was not included in the primary scoring system. When the pathergy test was done, however, an extra point may be given for a positive result. With four or more points, a diagnosis was determined.[12]

Clinical manifestations

Mucocutaneous

Mucocutaneous lesions are the most common during presentation and are frequently the earliest signs of the disease. They may occur several years before the diagnosis of BD.[16]

The cutaneous manifestations considered within the latest ICBD criteria in 2014

Oral ulcers

Oral ulcers which have a sensitivity of 98% and a specificity of 35%. They get two points. They are the most prevalent lesions, occurring in about 97 percent of patients and usually occur before the diagnosis of BD.[5] Before being diagnosed with BD, many individuals will have previously been diagnosed with complex recurrent oral aphthosis. They are well-defined, painful, punch-like and recurrent (three incidents per year). Gums, oral mucosa, tongue, lips, hard and soft palate, throat and tonsils are the most commonly afflicted areas.[13] They were divided into 3 types.

Minor ulcers

They were less than 10 mm in diameter and heal without scarring in 4 to 14 days. They are most commonly found in the non-keratinized areas of the oral mucosa (floor of the mouth and lateral borders and anterior portion of the tongue). They normally heal without leaving scars.

Major ulcers

≥10 mm, less frequent, deeper and more painful than minor ones, usually scarring and healing in approximately 2-6 weeks.

Herpetiform ulcers

2-3 mm can be solitary or grouped in clusters, pinhead morphology, superficial and painful.

The time between episodes varies from a few weeks to several months. They are seen less frequently in people who have had BD for more than 20 years and in those who have smoked in the past. Smoking cessation is linked to an increase in mucocutaneous symptoms as seen in ulcerative colitis patients.[14] Local trauma, certain foods and menstruation are other triggering causes. Multiple episodes of mouth ulcers in the early stages of Behçet's illness indicated that major organ involvement will develop in male patients. Because of the similarities to other types of oral ulcers, histopathologic study is of limited utility in differential diagnosis. At the ulcer's base, lymphocytes, macrophages and neutrophils can be observed. Around the vessels, the infiltration was more prominent.[15]

Genital ulcers

A sensitivity of 74% and a specificity of 94%. They score two points. They are the second most prevalent symptom, with 60-90 percent of patients experiencing them.[5] Genital ulcers resemble mouth ulcers in appearance; however they are usually larger, have irregular edges and are deeper. Ulcers are typically painful, shallow and well-defined, with an edematous border and a fibrin-covered yellow base.[16] Healing takes longer and scars are frequently hypo or hyperchromic; labia minora ulcers do not leave a scar. They usually resolve in 10-30 days in the absence of superinfection. Recurrence of genital ulcers is less common than recurrence of oral ulcers. The scrotum is the most prevalent site in men, followed by the penis and less frequently, the urinary meatus. The vulva, followed by the vagina and rarely, the cervix, is the location of most involvement in women, without affecting fertility. Epididymitis, salpingitis, varicocele,

vesicovaginal and urethrovaginal fistulas and other complications were possible.[17]

Dermal lesions

70 percent cumulative sensitivity and 87 percent specificity. They score one point. They are found in 40 to 90 percent of BD patients. Three cutaneous lesions are considered in this criterion erythema nodosum: sensitivity of 32% and specificity of 95%; pseudofolliculitis or papulo-pustular lesions (PPL): sensitivity 53% and specificity 92%. International criteria described them as pseudofolliculitis or papulopustular lesions or acneiform nodules in post-adolescent patients who have not received corticosteroid treatment, observed by a physician. It starts as an erythematous papule that evolves into a pustule within 24-48 hours. This description made it more difficult to diagnose BD because it also applied to folliculitis and acne vulgaris. The trunk, face and extremities are the most commonly affected areas. A perifollicular and perivascular infiltration of mononuclear and neutrophils is seen histopathologically.[17,18] Patients with BD are enrolled in one study and samples of papulopustular lesions and unaffected skin are taken. Biopsies of papulopustular lesions revealed considerable leukocytoclastic vasculitis compared to uninjured skin and significantly elevated IgM accumulation in the vasculature of the wounded skin, according to the findings. Injured skin had more IgG, C3 and fibrin deposition in the vessels than healthy skin, although the differences are not statistically significant.[19] PPL lesions are not sterile; *Staphylococcus aureus* and *Prevotella spp* have been isolated more frequently than in PPL lesions of acne patients.[20]

Skin ulcers

Skin ulcers have a sensitivity of 4% and a specificity of 98%, making them the most specific skin lesion. In the surrounding skin or in the rectum, genital-like ulcers might be seen (spectrum of manifestations).

Pathergy test: The pathergy test is optional and is not included in the main scoring system. However, when the pathergy test is performed, an additional point may be assigned for a positive result.

Ocular disease

The most prevalent ocular manifestation is acute uveitis, which occurs in 60-68 percent of patients, with panuveitis accounting for the majority. Acute uveitis is often bilateral, episodic, recurrent, non-granulomatous and is linked with retinal vasculitis, which can lead to blindness. Low vision, myodesopsias, red eye and eye pain are the most common symptoms.[21]

Neurologic disease

In 50 to 80 percent of cases, the most prevalent neurological symptom is headache.[22] BD typically affectes the central nervous system, with symptoms varying according on where it is located. Inflammatory lesions in the brainstem and basal ganglia causes brain parenchyma involvement in around half of the cases, hemispheric, spinal and meningoencephalitic manifest-ations also occur. Another distinct pattern is caused by vascular injury. It manifests as endocranial hypertension syndrome, which is caused by thrombosis of the cerebral venous sinuses.[23]

Vascular and pulmonary disease

The most common types of vascular involvement are superficial vein thrombosis and deep vein thrombosis, which impact 15-40% of patients. Both the upper and lower limbs may be affected and venous and arterial symptoms may coexist. In cases of pulmonary vessel involvement, aneurysms and pseudoaneurysms can be identified. If a pulmonary artery aneurysm ruptured, hemoptysis and cough also develop.[24] Lung illness usually manifested itself 3 to 4 years after the disease has begun. Thrombi in the pulmonary arteries are caused primarily by thrombosis *in situ*, rather than embolism, and are often accompanied by arteritis. Recurrences are reduced and remission is induced by immuno-suppression.[25]

Arthritis

Arthritis and arthralgia are common in people with BD and they are defined by recurrent, self-limited, non-deforming, non-erosive inflammation with an asymmetric pattern of inflammation. It can be mono or oligoarthritis, and it primarily affects the wrists, ankles and elbows.[26]

Gastrointestinal involvement

Gastrointestinal signs emerge 4.5 to 6 years after the onset of oral ulcers on average. The condition can affect any part of the gastrointestinal tract, from the mouth to the anus, but it is most common in the ileocecal region. It's difficult to tell apart from Crohn's disease. Symptoms range from mild to severe abdominal pain and can be accompanied by diarrhea, bleeding, vomiting, bowel habit change or weight loss. It has the potential to result in serious complications such as perforation or major bleeding.[27]

Renal disease

Kidney involvement in BD is mainly due to type AA amyloidosis, glomerulonephritis and renal vascular disease, with the most common clinical symptoms ranging from asymptomatic proteinuria and/or proteinuria to chronic kidney disease.[28]

Cardiac disease

Vasculitis causes cardiac involvement as well as the majority of systemic symptoms. Immune reactions mediated by T-type cells are directed at perivascular tissues. Perivascular inflammation can cause stenosis, thrombi and aneurysms and is seen in 7-46 percent of patients. Aneurysms in the coronary arteries can be observed, some of which are asymptomatic while others can cause an acute coronary syndrome. Patients have a worse prognosis than individuals who do not have cardiac involvement.[29]

Pathophysiology

Behcet's syndrome is a multifactorial systemic vasculitis with unknown etiopathogenesis. It has a strong geographic association as well as a genetic predisposition linked to the HLA-B51 factor and it involves interactions between genetic and environmental variables. It straddles the line between inflammatory and immunological illnesses as it has many of their characteristics. It, like other autoimmune illnesses, is characterized by activity triggered by antigen exposure such as infectious agents as a result of an abnormal immune response; nevertheless, it lacks antinuclear antibodies, female prevalence or an elevated likelihood of presenting other autoimmune disorders.[30]

Neutrophil activation, adaptive cellular and humoral immune system activation, toxic shock proteins, herpes simplex virus, streptococci, superantigens, linkage with HLA-B51 and vasculitic lesion have all been linked to immunopathogenic factors.[31]

Table 1: Summary of recommendations by EULAR in the updated consensus in 2018.

Affected organs	Treatment
Mucocutaneous	
Genital and oral ulcers	Topical steroids
Recurrent lesions with erythema	Colchicine
Papulopustular lesions (acne-like)	Same topical or systemic treatment as in acne
Eyes	
Posterior uveitis	Azathioprine, cyclosporine A, interferon alpha, anti-TNF monoclonal antibodies alone or in combination with glucocorticoids
Initial or recurrent sight-threatening uveitis	High-dose pulses of glucocorticoids, infliximab or interferon alpha
Isolated anterior uveitis	Isolated anterior uveitis
Deep venous thrombosis	Glucocorticoids, immunosuppressants such as azathioprine, cyclophosphamide or cyclosporine A
Refractory deep venous thrombosis	Anti-TNF monoclonal antibodies
Arterial involvement	
Pulmonary arterial aneurysm	High doses of glucocorticoids and cyclosporine
Refractory cases	Anti-TNF monoclonal antibodies
Aortic and peripheral aneurysms	Cyclophosphamide and glucocorticoids prior to surgery. Delay surgery if asymptomatic
Gastrointestinal involvement	Confirm with endoscopy or imaging studies
Severe or refractory gastrointestinal involvement	Glucocorticoids and mesalazine or azathioprine in acute exacerbations; anti-TNF monoclonal antibodies and/or thalidomide
Joint disease	
Acute arthritis	Colchicine
Monoarticular disease	Intra-articular glucocorticoids
Chronic or recurrent cases	Azathioprine, interferon alfa, TNF-alpha inhibitors
Central nervous system involvement	
Parenchymal disease	High doses of glucocorticoids and immunosuppressants; avoid cyclosporine
Severe and/or refractory cases	Anti-TNF monoclonal antibodies
Cerebral venous thrombosis	High doses of glucocorticoids, anticoagulants

Although no virus had been identified as the origin of the disease, *Herpes simplex* virus DNA has been found in oral and genital ulcers, along with high titers of antibodies against the virus and injection of the virus in mice has been shown to generate ulcer-like BD lesions.[32]

It has been reported that the disease occured after *Streptococcus agalactiae* vaginitis or *S. aureus* gingival infections, that there is an increased incidence of oral manifestations after dental treatments, that those affected usually have poor oral hygiene, that there is a higher prevalence of atypical streptococcus species in oral flora,

and that symptoms improved after antibacterial treatments.[33]

The link between heat shock protein 65kD (HCP 65) and antibodies identified in BD has been documented by Lehner et al since 1991. HCP-60 is an evolutionarily conserved molecule that shares a 50 percent homology with HCP-65, which is found in mycobacteria and streptococci. This protein, which is produced in mitochondria and translocated to the cell membrane during stress, has been identified as an endothelium autoantigen and a possible risk factor for atherosclerosis. The presence of anti-HCP antibodies with cross-reactivity with antigens in the oral epithelium of BD patients provides the greatest evidence of mimicry.[34]

As one of the key cells in charge of innate immunity, neutrophils exhibited abnormalities such as hyperactivation, enhanced chemotaxis, phagocytosis, superoxide formation and myeloperoxidase production. Increased production of IL-8, INF gamma and TNF alpha by lymphocytes such as Th17 is linked to the pathophysiology; other cells involved in hyperactivation are antigen-presenting cells, which produce IL 18. Neutrophil infiltration is seen in specific lesions in arterial and venous arteries.[35]

T lymphocytes appeared to have a role in the etiology of BD, with infiltration at pathergy sites and oral ulcers, a predominance of Th1 subpopulations and an immunosuppressive therapeutic response that suppressed T cells.[36]

Treatment

The current treatment is customized and focused on each distinct manifestation of the disease due to the considerable heterogeneity and various afflicted systems. The key recommendations of The European league against rheumatism (EULAR) in the updated consensus in 2018 are shown in Table 1.[37]

CONCLUSION

BD is a chronic and complex systemic disease that primarily affects young adult men. It has a multifactorial etiology and causes involvement of vessels of any size, resulting in a variety of symptoms, primarily mucocutaneous, with recurrent painful ulcers in the mouth and genitalia. It also causes skin lesions and is accompanied by other systemic manifestations such as ocular, pulmonary, cardiovascular, neurologic and renal disease. Because diagnosis is frequently delayed, we compiled a review of the diagnostic criteria available for its diagnosis as well as a description of the disease's pathophysiology and clinic knowledge. Because there is no pathognomonic laboratory test for BD, a basic understanding of the pathophysiology and clinical features allows us to recognize atypical presentations and distinguish them from other diseases with inflammatory and/or autoimmune behavior that can mimic Behcet's disease, reducing the time to diagnosis and minimizing the likelihood of sequelae.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Reyes-Weaver DA, Plata-Jimenez KL, Melo-Acevedo R. Behcet's disease: a review. Int J Res Med Sci 2022;10:279-84.