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Behçet's Disease : A Clinical Review

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Abstract

Behcet's disease (BD) is a rare relapsing systemic inflammatory disorder with a chronic, relapsing-remitting course of unknown etiology, current knowledge suggests that BD could follow an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals. BD has been hallmarked predominantly by oral aphthosis, genital ulcers, and chronic relapsing bilateral uveitis, all of which represent the "stigmata" of disease. However, many other organs including the vascular, neurological, musculoskeletal, and gastrointestinal systems can be affected. 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 diagnosis of BD is only supported by clinical criteria and requires 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. 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: Behcet's disease, auto-inflammatory, systemic vasculitis, Infliximab.

1. Introduction

Behcet disease (BD) was initially discovered by a Turkish dermatologist Hulusi Behçet in 1937 who identified three patients with oral and genital ulcerations, uveitis, and erythema nodosum. Many physical symptoms were later described, and added to the spectrum of disease [1]. BD is an auto-inflammatory systemic vasculitis of obscure etiology. Recurrent oral ulcers, genital sores, and ocular lesions usually used to characterize BD; however many other organs including the vascular, neurological, and musculoskeletal systems as well as the gastrointestinal system can be involved. In addition, this disease is also known as Behçet syndrome and malignant aphthosis [2-4].

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2. Epidemiology

Behcet disease usually has an onset in the third decade of life and is rare before puberty or after 50 years of age. It is believed that BD affects more males than females, in a proportion that varies from (1.5-5:1), and is in general more serious in male patients. However, a series of western studies (which included Brazilian studies) revealed a female predominance, but with less intense manifestations. Factors that modulate this clinical expression are still unknown [5]. A male predominance is observed in Arab populations while female predominance is evident in Japan, Korea, China, the United States, and some northern European countries. The disease has a more severe course in males and younger population. [6-10] BD has significant regional differences, with highest incidence in the Mediterranean, the Middle East, and the Far East **[11]**. 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 30° and 45°Nin Eurasian populations. Global distribution of BD is schematized in Figure(1) [12-14]. The incidence of BD varies according to geographical location, and does not follow Mendelian rules as shown by family studies [13]. The highest prevalence is found in Turkey, with up to 420 per 100,000 persons affected. Iran, Israel, northern China, and Korea follow with the next highest prevalence [14]. 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 [15,16]. The prevalence of BD have been reported (per 100 000 inhabitants) to be 13.5 in Japan [17]; 19.5 in Saudi Arabia, 15.2 – 120/100 000 in Israel, 2.1/100 000 in Kuwait, 17 in Iraq and 7.6/100 000 in Egypt [18]; 80 in Iran [19], 14 in China [20], Within Europe, the reported prevalence (per 100 000 inhabitants) trends higher among people in the Mediterranean area; Italy 2.5, Spain 7.5 and France 2.4 excluding immigrants [21,22].

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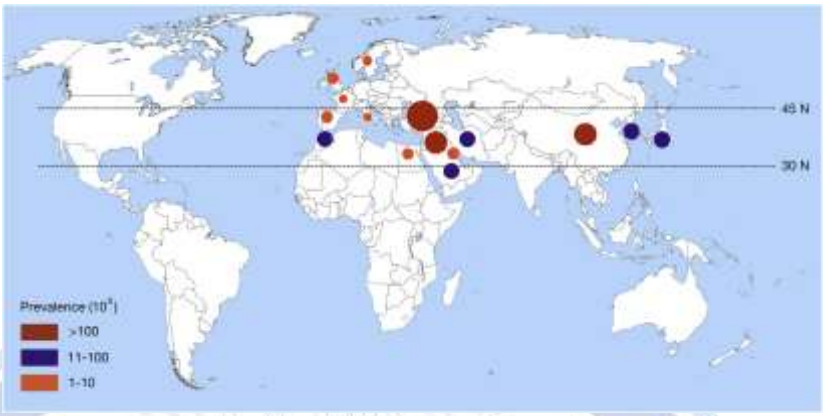

Figure (1): Global distribution of Behçet's disease [14].

3. Etiopathogenesis

BD has unknown causes; current knowledge suggests that BD could follow an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals [23].

3.1 Genetic

Four aspects demonstrate the genetic influence on BD susceptibility: peculiar geographical distribution, familial aggregation, correlation with HLA-B51 class I antigen, and polymorphisms in genes that control immune responses. HLA-B51 allele located in the major histocompatibility complex (MHC) locus on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route; a stronger association has been described in Turkish and Japanese patients compared to Caucasians [12]. Studies have shown that HLA-B*51 is associated with BD, with more than 60% of patients testing positive for HLA-B*51[24].

Other genes present in the MHC locus have been studied like HLAB5701, 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 [25].

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) and encoding interleukin 12 receptor beta (IL12B2) genes were strongly associated with BD [26]. 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 no do sum-like skin lesions in patients with active BD [27]. 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 [28]. 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 [29]. Recently, the study of [30] was reported that a high percentage of patients with BD have one or several variants in AID genes. Additionally, they suggest that the association of MEFV with BD could be modulated by the HLA molecules; whereas the protective effect of the loss of function of NOD2 p.Arg702Trp polymorphism would be independent of HLA. Behcet's disease has been shown to be associated with genotoxicity as measured by cytogenetic and oxidative DNA damage assays. For example, elevation in sister chromatid exchange (SCE) in BD lymphocytes has been shown by several reports [31]. The increase in the SCE rate was evident in patients with active and inactive episodes and in patients typed positive or negative for HLA-B51allele. The mechanism for this genotoxicity is still not clear, however, significant elevation in the oxidative damage biomarkers such as 8-hydroxy deoxyguanosine, plasma malondialdehyde and protein carbonyl was detected in BD patient's [32]. In addition, levels of ascorbic acid and antioxidant enzymes that include catalase, glutathione peroxidase and superoxide dismutasewere relatively lower in BD patients than in healthy controls [33].

3.2 Infection

Infectious agents have long been proposed as triggering factors in BD development. A number of bacterial and viral microorganisms have long been postulated as possible environmental triggers of BD, specially Herpes simplex virus-1 and Streptococcus Sanguis [12,34]. 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 [35]. Several Streptococcus strains have become increasingly important in infectious etiology. The development of some clinical manifestations of the disease in hypersensitivity tests against streptococcal antigens is one of the most relevant evidences [36]. In addition, antibodies against S. sanguinis and S. pyogenes were obtained more frequent in BD patients than in controls [37]. Streptococcal 65-kDa HSP from an uncommon serotype (KTH-1, strain BD113-20) of oral S. sanguinis has been reported to be an important trigger in the pathogenesis [14]. Neurofilament medium (Nf-M) was recently suggested as possible antigen able to trigger an immune response via molecular mimicry with bacterial HSP-65 [38]. Immunoglobulin M in BD patients has been reported able to react with some streptococcal proteins such as streptococcal a-enolase and glyceraldehyde 3-phosphate dehydrogenase [39]. Cho et al. demonstrated that the S. sanguinis GroEL protein is a target of the serum anti-S. sanguinis IgA antibody. In addition, serum IgA reactivity against recombinant S. sanguinis GroEL has been correlated to reactivity against recombinant human hnRNP A2/B1 suggesting how autoreactive lymphocytes may be activated by infectious triggering [40]. As BD usually starts from the oral mucosa, it has been speculated that oral microbial flora may be implicated in the pathogenesis of the disease [41]. BD patients can develop newonset oral ulceration or experience both cutaneous and systemic flare-ups following dental

procedures or surgical treatments for chronic tonsillitis [42]. Antimicrobial agents have been used successfully for treating various disease symptoms [43]. Several previous studies and our experience showed oral health impairment in BD patients compared with healthy subjects [44,45]. Oral health improvement in BD patients may positively modify their disease course. Dental treatments in BD patients could be associated with a relapse of oral aphthae in the short time but could decrease their number in longer follow-up (_6 months) [46], also leading to better oral health in the long-term follow-up. Higher levels of various Streptococci were found in the oral mucosa of BD patients. In addition, S. sanguinis strain resulted able to induce the secretion of inflammatory cytokines by the KTH-1 cells. It is plausible that an inflammation process induced by infectious agents in subjects with predisposing genetic background leads to the development of BD [47,48]. Several studies have investigated the association between HSV-1 and BD. Herpes Simplex Virus (HSV) type 1 can be detected in saliva, intestinal ulcers, and genital ulcers by polymerase chain reaction (PCR) in patients with BD compared with healthy controls [49,50]. 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 [51]. Studd et al. in an situ DNA-RNA hybridization method, detected a higher frequency of hybridization between HSV-1 DNA and complementary RNA in mononuclear cells of BD patients compared with healthy controls. The results show the presence of at least a portion of the HSV-1 genome in mononuclear cells of BD patients [52]. Cytomegalovirus, Epstein-Barr virus, Parvovirus B19, Varicella zoster virus, Hepatitis virus have also been investigated as possible triggering factors but these studies were characterized by low-level evidences [53,54]. Recent studies have shown that the differences in salivary or gutmicrobiome compositionmay have a role in the pathogenesis. In a study of the salivary microbiome using high- throughput sequencing of the 16S rRNA V4 region, Coit et al. reported that BD patients have a significantly less diverse microbial community structure than healthy controls [55]. In another study, Consolandi et al. compared the fecal microbiota of BD patients to healthy controls. They reported both a peculiar dysbiosis of the gut microbiota and a significant decrease of butyrate production in BD patients. Authors speculated that a defect of butyrate production might lead to both reduced T regulatory cells (Tregs) responses and activation of immunopathological T-effector responses [56]. To date, the most generally accepted theory to explain the effect of infectious agents in BD is the high homology that some microorganism antigens may have with human proteins, such as that of heat shock protein (HSP 65) obtained from Mycobacterium, with human protein (HSP60); this cross-reaction may lead to the onset of an immune response [57]. Research on genes related to apoptosis have not shown conclusive results.

3.2 Immunity

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, thus linking their presence to the pathogenesis of the condition [58]. Lee, et al. [59]

identified α-enolase as a target antigen of IgM-type 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[14]. Activated innate immunity plays an important role in the pathogenesis of BD. Microbial triggers are sensed and processed by the innate immune system via pathogen-related and/or danger-associated molecular patterns. Overproduction of inflammatory cytokines by innate immune cells such as macrophages and dendritic cells may cause a higher production of adaptive Th1- and Th17-related cytokines. BD lesions in their early stages are predominated by neutrophils which have a predominant role in the innate immunity system, and abnormalities in their activity have been extensively reported in BD patients. The priming state of neutrophil has been reported in vivo among BD patients, and the role of T cells in the neutrophil activation has been shown in experimental studies. Elevate concentrations of proinflammatory cytokines including IL8, INF γ and TNFα may be responsible for the prime state of neutrophils [60]. 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 levels of IL8 were reported in serum of BD patients, as well as in skin lesions and small vessel endothelial cells, correlating IL8 with disease activity and vascular involvement [61,62]. Neutrophil are directly involved in specific lesions of BD as histopathological analysis of BD lesions showed venous and arterial infiltrates of neutrophils. On the basis of this evidence, it has been proposed to classify BD. Surface molecules, indicating neutrophil activation status (CD10,CD14, and CD16), oxidative burst and phagocytic function of neutrophils have been explored and the presence of proactive neutrophils in BD patients was reported [63]. Tissue injury in BD can be modulated by neutrophils in several manners: neutrophils were hyperactivated, probably HLA B_51-associated, and usually were involved in perivascular infiltration [64]. Recently, Yavuz et al. reported that testosterone causes a significant neutrophil activation together with Th-1 type immune alterations which may explain a more aggressive disease with a higher mortality rate in male BD patients [65].

Another member of innate immunity, natural killer (NK) cells are also found in BD lesions [66]. NK cells were also identified in BD lesions where seems they have a role in driving the CD4+ Th1 response which is the main feature of BD lesions [67,68]. However, several studies underlined increased NK cells in the peripheral blood, in particular during the active phases of the disease [69,70]. Dysregulation of the immune system contributes to BD etiopathogenesis, with increased systemic levels of inflammatory cytokines [69]. T cell subpopulations γδT cells and cytotoxic T cells, Th1 T cells, regulatory T cells (Tregs) and Th17 cells have been shown to have a role in the pathogenesis of BD [71]. γδ T lymphocytes act as the first line of host defence in mucosal immunity. An increased proportion of activated γδ T cells has been shown in BD [72,73], suggesting a role for them in the pathogenesis of the disease [74]. Furthermore, accumulation of γδ T cells in the sites of inflammation in BD has been

reported [75]. It's well known that CD4+T cells can differentiate into two types: Th1 cells subset, which secretes IFN-g, IL-2, and TNF and promotes cell-mediated immunity, and Th2 cells, which produce IL- 4, IL-5, IL-10, and IL-13 and promote antibody-mediated immunity [76]. The alteration of T cell balance, especially Th1/Th17 expansion and decreased regulation by Tregs, are supposed to have a significant role in BD pathogenesis [77,78]. In particular, increased frequencies of Th17 cells were reported in the BD cutaneous lesions [79]. Th17 and IL-17 pathways might have a part in the development and/or activity of BD [80]. IL-17 levels of BD patients with active stages of uveitis, oral and genital ulcers and articular symptoms were significantly higher compared with patients with inactive stages of the same symptoms. Hamzaoui et al. demonstrated that the percentage of circulating Th17 cells and plasma interleukin IL-17 levels were increased in active BD [81,82]. Takeuchi et al. compared the proinflammatory and Th1-, Th2-, and Th17-related cytokines frequency in a group of BD patients with recurrent uveitis and a group of remitted uveitis before and after infliximab treatment. They found higher levels of IL-1b, IL-4, IL-17A, IL-17F, IL-21, IL-22, IL-31, IFN-g, sCD40L, and TNF-a, with a significant difference for IL-17F, in BD recurrent uveitis patients respect to the BD-remitted uveitis group, before drug infusion. In addition, only IL-10 levels were found higher in the remission group than in the other group [83]. Emmi et al. showed that cytotoxic Th1 and Th 17 cells can play a role in inducing mucosal damage during the early stages in BD patient with active intestinal involvement [84]. These results confirm that Th17 and IL-17 pathway are active and play an important role, particularly in acute attacks of the disease. Conversely, a reduction in Tregs and cytokine IL-10 were notified in the disease [85]. Due to recent progress in molecular methods and basic scientific researches, our knowledge about the disease has considerably increased. GWAS have become a very important step in understanding BD pathogenesis. New genes such as ERAP1 have been introduced which help to understand the possible pathogenic mechanism of HLA-B_51. In the future, similar studies in different populations with a higher number of patients will provide significant advances in the etiopathology of BD. Despite all these advances, clinical expression of the disease is quite heterogeneous and show regional differences. The underlying environmental and genetic factors of this situation are not fully elucidated. Being a complex disease, BD is related more than one pathogenic pathway. Although, management of the disease has evolved noticeably because of more effective and targeted therapies we still need new treatment options for severe and non-responsive cases such as biological treatments developed for the underlying etiopathological mechanism [86].

4. 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 [87]. Other clinical manifestations that may present through the course of the disease include audiovestibular, cardiovascular, pulmonary, gastrointestinal, central nervous system, dermatological and joint disorders. As there are no pathognomonic clinical or laboratorial findings of BD, several diagnostic criteria

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have been developed during the years, all having in common the 3major 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 [88]. The pathergy test is the non-specific hyper activity of the skin following minor trauma and is a unique feature of BD [89]. It consists of the intradermal puncture of the skin with a 20-gauge or smaller needle 5mmobliquely 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 [90,91]. A study demonstrated that surgical cleansing of the skin before the puncture reduced the test positivity [92]. Differential diagnosis plays a relevant role in BD. BD diagnosis is only supported by clinical criteria that require the exclusion of other diagnoses based on clinical presentation. Oral ulcerations may occur in 30–40% of the general population, and therefore cannot be considered specific of BD; 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 [93] and Cogan syndrome [94] 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 [95]. Lastly, chronic inflammatory bowel disorders must be ruled out in case of gastrointestinal involvement [96]. When audiovestibular symptoms are present we must consider differential diagnosis with SSHL [97] and Meniere's disease [98].

5. Management

Treatment options depend on the affected organ and its severity. It is important to prioritize therapeutic options according to the disease type, severity, age, and sex of each patient. Special attention should be paid to ocular, vascular, and neurologic disease, because they are the most serious manifestations and require more aggressive treatment.

Corticosteroids

Topical corticosteroids are beneficial for oral and genital ulcerations, and can be the first-line treatment, especially for patients with mild disease, while systemic corticosteroids are the recommended treatment for patients with moderate to severe disease with ocular, vascular, gastrointestinal, or neurological involvement [99] Although corticosteroids are widely used for patients with Behçet’s disease, there has been only one placebo-controlled trial, in which 86 patients who had active disease with

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genital ulcer were randomized for administration of either intramuscular methylprednisolone 40 mg or placebo every 3 weeks for 27 weeks.

Colchicine

Colchicine has been used for the treatment of Behçet's disease, particularly for mucocutaneous disease. The antiinflammatory effect of colchicine has been attributed to its disruption of microtubules in neutrophils, thereby inhibiting their migration toward chemotactic factors. In one randomized controlled trial, use of colchicine significantly reduced the rate of genital ulcers, erythema nodosum, and arthritis associated with Behçet's disease, especially among female patients [100].

Azathioprine

Azathioprine is a purine synthesis inhibitor and one of the most widely used immunosuppressive medications for Behçet's disease. In the only placebo-controlled trial, 73 patients who had Behçet's disease with or without ocular involvement, were randomly assigned for treatment with either azathioprine (2.5 mg/kg/day), or placebo. After 2 years of follow-up, the patients taking azathioprine developed less ocular disease and experienced less frequent ocular complications, oral ulcers, genital ulcers, and arthritis [101]. A retrospective analysis of 157 consecutive patients with severe uveitis (active posterior uveitis or panuveitis) treated with corticosteroids (0.5–1 mg/kg/day) and azathioprine (2.5 mg/kg/day) revealed that posterior uveitis was controlled in 92.9% of patients, of whom 51.6% were complete responders and 41.4% were partial responders [102].

Thalidomide

Thalidomide was developed in the 1950s as a sedative drug and was withdrawn in 1961 because of its teratogenic effects. However, it has been rediscovered recently as an immunomodulatory drug that suppresses tumor necrosis factor (TNF)-α-induced nuclear factor (NF)-κB activation and adenosine triphosphate (ATP)-induced interleukin (IL)-1β secretion [103]. By modulating the activity of NF-κB, thalidomide can up-regulate the expression of downstream genes involved in the pathophysiology of Behçet's disease. Thalidomide has been reported to be effective in treating patients with mucocutaneous lesions [104]. Cyclophosphamide Although a systematic review of the Cochrane database concluded that there was not enough evidence to support the use of cyclophosphamide in the treatment of Behçet's disease, particularly the ocular manifestations [105], it still can be a choice for life-threatening manifestations.

Tumor necrosis factor-α inhibitors

Evidence is emerging that anti-TNFα agents are highly effective for patients with Behçet's disease. Among them, infliximab has been most frequently used, mainly for refractory ocular Behçet's disease. Although there have been no controlled trials, a considerable number of observational studies have reported that infliximab reduces the frequency of uveitis attacks, successfully treats refractory macular edema, and improves visual acuity [106]. Only one prospective study from Japan has evaluated the

efficacy of infliximab, using 3–5 mg/kg body weight every 8 weeks in patients with gastrointestinal disease. In this study, all patients showed improvement of gastrointestinal symptoms and disease-associated complications within 4 weeks. Furthermore, the rate of disappearance of ileocecal ulcerations was 90% after 1 year [107].

Conclusion

BD is a complex syndrome characterized by significant heterogeneity of clinical manifestations with usually frequent relapses. The etiology of BD is still obscure: it is believed to be due to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals. As there are no laboratorial findings of BD, the diagnosis is only supported by clinical criteria. Nevertheless, a careful evaluation of endoscopic findings may help in the diagnostic interpretation, whereas the endoscopic biopsy is necessary to confirma histopathologic diagnosis. The management of Behçet's disease has markedly improved, with better use of conventional medications and the development of newer agents such as biologics. The main goal of treatment should be aimed at avoiding and preventing the feared complications of BD that endanger the life of these patients. Despite tremendous research success. There are still many gaps that need to be fulfilled, future studies should be directed to the possibility of studying the effect of oxidative stress on the development of the disease and the appearance of symptoms in patients in addition to studying the genetic and epigenetic changes to determine the most important causes of BD especially in Iraqi population.

Conflict of Interests.
There are non-conflicts of interest .

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الخلاصة

يُعد مرض بهجت من الاضطرابات الالتهابية الجهازية النادرة التي تنتشر بمسارات مزمنة متكررة غير معروفة الاسباب. تقترح الدراسات الحالية ان مرض بهجت ممكن ان يكون بسبب المناعة الذاتية للجسم ضد تجاه بعض العوامل المعدية او العوامل البيئية لدى الاشخاص المؤهلين وراثيا للاصابة. يتم تمييز المرض غالبا بوساطة التهاب الفم , القرحة التناسلية والتهاب العنبية المزمن ,وكلها تكون بمثابة "بصمة" للمرض . ومع ذلك، يمكن أن تتأثر العديد من الأعضاء الأخرى بما في ذلك الأجهزة الوعائية والعصبية والعضلية الهيكلية والجهاز الهضمي. يحدث مرض بهجت بشكل متكرر في السكان الأوراسيين على طول الطريق التجاري القديم المعروف باسم "طريق الحرير" الذي يمتد من شرق آسيا إلى حوض البحر الأبيض المتوسط. يتم تشخيص مرض بهجت من خلال المعايير السريرية فقط ويتطلب استبعاد التشخيصات الأخرى بناءً على الاعراض السريرية. لا توجد فحوصات مختبرية خاصة بهذا المرض. غالبًا ما يؤدي هذا المرض النادر إلى العمى واعتلالات جهازية مميتة. تشمل الأسباب الرئيسية للوفاة أمراض الأوعية الدموية الرئيسية واعتلالات الجهاز العصبي المركزي. تُستخدم الكورتيكوستيرويدات بشكل شائع لعلاج المظاهر السريرية لمرض بهجت مع أدوية مثبطة للمناعة. من العلاجات التي سجلت نجاحا في علاج مرض بهجت هو TNF مثل Infliximab و Etanercept و Adalimumab .