An Insight about Behcet's disease; Pathogenesis, Presentation and Management

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Abstract

Background: Behçet's disease (BD) is a variable vessel vasculities that involves several organs and systems, causing ulcers on the oral, genital and intestinal mucosa, skin lesions that are most commonly in the form of papules, pustules or nodules, arthritis, uveitis, central nervous system lesions, venous and arterial thrombosis and arterial aneurysms. The exact pathogenic picture of BD is far from being clear. Whether it should be classified as an autoimmune or an auto inflammatory condition had been extensively debated. Early theories pointed to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals. Behçet disease, a chronic recurrent systemic inflammatory vascular disease, may affect blood vessels of any type and size. The disease can present with variable clinical manifestations and the most commonly involved systems are oral, ocular, cutaneous and urogenital. The diagnosis of BD is mainly based on clinical manifestations after ruling out other potential causes. There is no specific laboratory, histopathological, or genetic findings for the diagnosis of BD. Furthermore, there is a large geographical variation both in the disease prevalence and the disease manifestations. Therefore, the diagnosis of BD may be difficult in patients presenting with only major organ involvement such as posterior uveitis, neurologic, vascular, and gastrointestinal manifestations. The emergence of other disease manifestations aiding the definite diagnosis of BD can take months and even years in this group of patients. The disease can also remain limited in some patients, which causes diagnostic difficulty. BD typically runs in a relapsing and remitting course, and the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage, A coordinated multidisciplinary approach is necessary for optimal care, treatment choices should be individualized based on age, sex, type, and severity of organ involvement as well as patient preferences. Ocular, vascular, neurological, and gastrointestinal involvement may be associated with a poor prognosis. Given the clinical heterogeneity of BD, the therapeutic approach is highly variable and is guided by the predominant disease manifestation

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Behçet's disease (BD) is a variable vessel vasculities that involves several organs and systems, causing ulcers on the oral, genital and intestinal mucosa, skin lesions that are most commonly in the form of papules, pustules or nodules, arthritis, uveitis, central nervous system lesions, venous and arterial thrombosis and arterial aneurysms. The prevalence of Behçet's disease varies geographically, with the condition being most common

along the ancient "Silk Road" route extending from Mediterranean countries such as Turkey and Iran to the Far East including Korea and Japan where the prevalence of human leukocyte antigen-B (HLA-B*51) is relatively high, compared to the rest of the globe. Reported prevalence has found to be as high as > 1 case per 1000 population in Turkey **(1).**

However, over the last 50 years, BD has been more widely recognized worldwide. In Western Europe, prevalence has been reported at 7.5, 7.1 and 1.1 per 100 000 population in Spain, France and Germany, respectively. In comparison, there have been relatively few attempts at estimating the prevalence of BD within the UK. The most recent estimates come from over 20 years ago, and range from 0.27 to 0.64 per 100 000 population. The prevalence of BD in Egypt is 3.6/100,000, with no remarkable north-to-south gradient but rather there is a higher concentration of cases in the big cities. The male-to female ratio is 2.6:1. Sex driven influence on the disease phenotype was notable unlike the effect of the age at disease onset. While, the CNS, DVT, and GIT involvement are higher in males, the joint affection and disease activity were increased in females **(2).**

Pathogenesis:

The exact pathogenic picture of BD is far from being clear. Whether it should be classified as an autoimmune or an auto inflammatory condition had been extensively debated. Early theories pointed to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals, innate and adaptive immune mechanisms playing a role in the chronification of disease pathogenesis and tissue damage **(3).**

Genetic susceptibility in Behçet's disease:

A. The major histocompatibility complex I (MHC I) and HLA-B* 51 and its association with BD:

The MHC, also known in humans as the human leukocyte antigen (HLA) , region encodes several molecules that play key roles in the immune system. A strong association was established between the HLA regions and autoimmune disorders. A meta-analysis based on 72 studies in 74 study populations revealed the moderate association of HLA-B5/-B*51 with male gender, the high prevalence of eye involvement, skin involvement, and genital ulcers, and low prevalence of gastrointestinal involvement **(4).**

B. Other MHC/HLA associations:

Meanwhile, multiple HLA-related gene variants also play essential roles in BD, including variants in the class II major histocompatibility complex transactivator (CIITA), endoplasmic Reticulum Aminopeptidase 1 (ERAP1) and the major histocompatibility complex class I chain related gene A (MICA) **(5).**

B.1. CIITA:

The HLA class II transactivator gene (CIITA), encodes an important transcription factor that regulates the MHC class II genes, IL-4, IL-10 and other immune-mediating genes. CIITA is implicated in various autoimmune and autoinflammatory diseases. In a study of a Chinese Han population, the GG genotype and G allele of the CIITA gene (rs12932187) were correlated with risk factor for BD, and the GG carriers had a higher expression of the CIITA gene **(6).**

B.2. ERAP1:

ERAP1 is an important enzyme that trims peptides for binding onto MHC class I molecules. Single nucleotide polymorphism (SNP) rs17482078 inERAP1 was found as a risk factor for BD in a Turkish genome-wide association study (GWAS) and the finding was replicated in Iranian. Moreover, SNP rs10050860, rs1065407, rs2287987 and rs2013717 in ERAP1 were also associated with BD in a Chinese GWAS study **(7).**

B.3. MICA:

The major histocompatibility complex class I chain related gene A (MICA) is a gene that functions in immune activation under cellular stress conditions, such as infections, tissue injury, pro-inflammatory signals, and malignant transformation. The (MICA) is located in proximity and in between the HLA-B and tumor necrosis factor (TNF) genes on the short arm of chromosome 6. It has long been considered a major genetic susceptibility gene for BD and has been studied in many different populations. The MICA*006 (MICA-A6) and MICA*009 alleles were associated with BD susceptibility in the HLA-B*51 positive Turkish population. MICA-A5.1 was indicated a negative correlation with ocular lesions and iridocyclitis in BD patients (**8)**

C. Non-MHC I susceptibility genes:

c.1. Interleukin (IL) family genes:

Although HLA-B*51 is the known genetic factor most closely associated with BD, it accounts for <20% of the genetic risk. A GWAS and meta-analysis identified common variants in interleukin 10 (IL-10) and at the IL-23R–IL-12RB2 locus that predispose individuals to BD **(9.**

Interleukin-10 (IL-10) is a widely expressed cytokine that contributes to preventing inflammatory and autoimmune pathologies. Multiple cells of innate and adaptive immune system exert important functions in BD, including CD4+T cells, CD8+ T cells, dendritic cells, macrophages, NK cells , neutrophils and B cells, and almost all of them could express IL-10. IL-10 was identified as risk locus for many inflammatory diseases, including BD. Multiple SNPs of IL-10 were confirmed to be strongly associated with BD. IL-18 is a proinflammatory cytokine that mediates T-helper (Th-1) immune responses. IL-18 gene −607 promoter site polymorphism was associated with patients with BD in Egyptian patients. Moreover, they found GG genotype at position −137 had a higher risk of developing ocular manifestations in patients with BD **(10).**

IL-33 is a member of the IL-1 cytokine family that expressed by various types of immune cells such as mast cells, macrophages and dendritic cells, that drives production of Th2-associated cytokines. A significantly higher prevalence of the IL-33 SNP rs1342326 T/G was found to be in BD patients. Studies showed also this genotype was also associated with increased IL-33 expression in patients with BD compared to healthy controls **(11)**.

c.2. other genes:

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway exerts important functions in multiple immune-mediated diseases. Tofacitinib, a JAK1/3 inhibitor targeting T cell signaling, was shown to be effective for BD patients**.** Another study demonstrated that multiple SNPs of JAK1 contributed to the genetic susceptibility of BD with ocular involvement, including rs2780815, rs310241,rs3790532. STAT4 belongs to the STAT family that regulate s gene transcription in response to type I interferon (IFN-I) and various cytokines of IL family. STAT4 has been implicated in T-helper cell differentiation, natural killer (NK) cell activation and IFNg production and contributes to multiple inflammation and autoimmune diseases **(12).**

II-Environmental factors in Behçet's disease:

Like in the most of autoimmune conditions, the genetic component does not suffice to explain disease occurrence. Rather, environmental triggers seem to play a crucial role. Although far from being clear, current evidence points to infectious agents as environmental triggers for BD**.** Different microorganisms have been postulated to elicit a self-reactive immune response in genetically predisposed individuals due to the presence of conserved motifs or high homology with human proteins (molecular mimicry) **(13).**

This cross-reaction has been attributed to a wide range of organisms, from streptococci species, Helicobacter species or mycobacteria to even herpex virus or parvovirus. Large differences among these groups keep away the possibility of a single, specific etiology trigger, and reinforce the hypothesis of conserved peptides that may be loaded in the HLA-B51 molecule with different affinities and presented to T-cells **(14).**

III- Immune system dysregulation:

Innate immunity:

The innate immune system, (nonspecific immune system) represents the first line host defense against pathogens. The main actors of this first defense are macrophages, dendritic cells (DCs), Polymorphonuclear (PMN) neutrophils. These cells represent receptors on their membrane surfaces; pattern recognition receptors (PRRs), which recognize molecules, distinct from the host ones and shared by different pathogens. PMN neutrophils which play an important role in innate immunity and in BD pathogenesis can be activated both by antigen presenting cells (APC) and T cells. PMNs hyper activation is confirmed by an increased expression of activation markers such as CD11a, CD10 and CD14 on cell surface **(15).**

Only few data are available about dendritic cells (DCs) and their possible role in the pathogenesis of BD. It has been demonstrated a decrease in percentage of peripheral plasmocytoid DCs (pDCs), probably due to their migration from circulation to target tissues during inflammation. The potential interaction of neutrophils,

monocytes, and DCs with γδ T cells in BD**.** An infectious trigger (e.g., microbes) results in extravasation of neutrophils and following phagocytosis of the invading microbes, neutrophils release traces of (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) into the microenvironment where γδ T cells sense it. Monocytes then might take up or bind this soluble HMB-PP and present it to γδ T cells. This interaction triggers tumor necrosis factor α (TNFα) secretion, a proinflammatory cytokine along with other similar cytokines including IFNγ which promotes γδ T cell expansion and drive local chemokine (C-X-C motif) ligand 8 (CXCL8) production that further recruits new neutrophils and monocytes to the site of infection. In addition, activated γδ T cells keep providing survival and activation signals to the newly recruited neutrophils and monocytes by secreting TNFα. Furthermore, activated γδ T cells present antigen to DCs and thus initiate Th1, Th2, and Th17 differentiation and proliferation. Even if the infectious trigger is in the form of a non-HMB-PP source such as HSP60/65, γδ T cells can again respond by expanding and keep the interaction active with the neighbouring cells **(16).**

Adaptive immunity:

The adaptive immune system (acquired immune system) is composed of highly specialized cells that involves a tightly regulated interplay between APC , T and B lymphocytes, which facilitate pathogen-specific effector pathways, generation of immunologic memory, and regulation of host immune homeostasis **(17).**

Clinical manifestations:

Behçet disease, a chronic recurrent systemic inflammatory vascular disease, may affect blood vessels of any type and size. The disease can present with variable clinical manifestations and the most commonly involved systems are oral, ocular, cutaneous and urogenital **(18)**.

I-Mucocutaneous manifestations:

The most common skin findings in BD **(3).**are oral and genital aphthous ulcers, papulopustular lesions (PPLs), erythema nodosum (EN)-like lesions and superficial thrombophlebitis **(19).**

1-Oral ulcers (OU):

Recurrent aphthous ulcers are seen in almost all patients during the course of BD. In most cases, oral aphthous lesions are the first manifestation of the disease, preceding the fulfilment of criteria for the diagnosis by 4–8 years. Clinically, oral aphthous ulcerations are classified as minor, major and herpetiform **(19).**

2-Genital ulcers:

Genital ulcers are the second most common symptom in BD and they present in 60%‑90% of the patients**.** Genital ulcers are preset in males mainly on the scrotum. Occasionally, lesions may occur on the penis, in the urethra in men or in the vulva and vaginal area in women. Although genital ulcers are virtually universal in Behçet‟s disease, Behçet‟s disease is a rare cause of genital ulceration. Causes of genital ulcerations other than BD including venereal diseases such as syphilis, chancroid, and herpes simplex viral infection, erythema multiforme and erosive lichen planus. Recurrent genital ulcerations may also be seen in hypereosinophilic syndrome, myelodysplastic syndrome, tuberculosis cutis, and acquired immune deficiency syndrome. Other rheumatic causes of genital ulceration include reactive arthritis and Crohn‟s disease **(19).**

3-Papulopustular lesions:

Papulopustular lesions are situated mainly on the lower limbs and they are seen as many as 34–70 % of patients with BD. Some of the papulopustular lesions of BD resembling the pustular lesions of acne vulgaris are called acneiform lesion of BD. The pathogenesis of pustular lesions of BD is attributed to vasculitis while those of acne vulgaris belong to sebaceous gland disorder under hormonal factors **(20).**

4-Erythema Nodosum-like lesions (ENLs):

EN lesions are characterized by 1 to 10 cm erythematous and tender subcutaneous nodules located over the extensor aspects of the lower extremities that resolve in 3 to 6 weeks without leaving any scars or atrophy. EN is associated with a wide variety of stimuli such as infections, sarcoidosis, Behçet's disease (BD), rheumatologic diseases, inflammatory bowel diseases, medications, and pregnancy . The pathogenesis of EN is not fully understood. EN most probably results from immune complex deposition in and around the veins of the connective tissue septa of the subcutis. ENLs manifest mostly in females. Other than lower extremities, ENLs are reported on the face and neck. The main difference between erythema nodosum and ENL is the existence of vasculitis and necrobiosis in the latter **(21).**

5- Pathergy test:

The pathergy phenomenon is a nonspecific hypersensitivity reaction to trauma. It can be performed by puncturing the flexor aspect of forearm skin with a 20-gauge needle **(19)** , and the test is considered positive if an indurated erythematous pustule develops at the site of trauma within 24 to 48 h. Pathergy reaction can be seen in pyoderma gangrenosum, Sweet's syndrome, deficiency of IL-1-receptor antagonist (DIRA) and Crohn's disease. There are also case reports of pathergy in atypical eosinophilic pustular folliculitis, neonates with Down's syndrome, myeloproliferative disorders, non-Hodgkin's lymphoma and chronic myeloid leukemia treated with interferon-α **(22).**

6- Sweet's syndrome like lesions:

Sweet syndrome-like lesions are single or multiple, erythematous nodules with or without pustules that mainly appear on the face, neck and hands. Some patients have been reported with generalized lesions involving the face, extremities and buttocks **(19).**

Although clinical and histological similarities exist between BD and such Sweet's syndrome as the presence of oral ulcer, arthralgia, arthritis, episcleritis, pathergy positivity and neutrophilic infiltrate in the dermis in both of the diseases, there are some distinctive features. In BD, the development of oral ulcer is more frequent, fever is rarely seen, the pattern of articular and ocular involvement is different. In addition, comparing two diseases by human leucocyte antigen (HLA) typing revealed that patients with BD had higher frequencies of HLA-B51 and HLA-Dqw3, while patients with Sweet's syndrome had higher frequencies of HLA-Bw4. Sweet's syndrome-like lesions have been reported to occur in the acute phase of BD or sometimes have been thought to point a flare in BD **(23).**

7-Pyoderma gangrenosum :

Pyoderma gangrenosum (PG) is a rare and chronic neutrophilic dermatosis. It is clinically characterized by aseptic ulcerations preferentially located in the lower limbs. Its location in the genital area is unusual and could be a source of diagnostic difficulties. In half of the cases, PG is associated with an underlying disease. The association with Behçet's disease is exceptional **(24).**

8-Other Skin Lesions:

Other skin lesions, such as extragenital skin ulcers in the axillary and inter-digital areas, palpable purpura, necrotizing vasculitic ulcers, hemorrhagic bullae, abscesses, erythema multiforme like lesions, subungual infarctions, are less common in BD **(25).**

II-Ocular manifestations:

Ocular involvement is seen in about 70% of patients who have BD. The entire uveal tract is at risk of inflammation, characterized as a nongranulomatous necrotizing obliterative vasculitis. It may initially begin unilaterally. However, it is usually a bilateral disease and the second eye soon follows. The usual age of onset is around 30 years of age and is often more severe in the male patients. t is a progressive sight-threatening disease that may involve parts or the entire uveal tract and may blind up to 25% of patients within a course of 10 years, after which disease progression tends to stabilize **(26).**

III-Musculoskeletal manifestations:

It has been reported that approximately 30–60% of Behçet's disease patients present with joint symptoms and is characterized to be recurrent, without deformity or erosions, mainly in large joints. Knees, ankles and wrists are among the most commonly involved joints, and up to 10% of the patients with articular involvement complain of inflammatory back pain too **(25).**

Joint involvement tends to be self-limited and spontaneously resolves in 2–4 weeks. Morning stiffness is uncommon and only mild inflammation can be found in the synovium **(27).**

IV-Vascular Involvement:

Vascular involvement is one of the major causes of morbidity and mortality in BS . Male gender and young age are associated with venous thrombosis in BS. Prevalence of vascular involvement among BS patients varies from 15% to 40% in different series. Unlike other systemic vasculitis, BS is characterized by coincident involvement of both arteries and veins of all sizes and presents a unique tendency for aneurysm

formation. It includes venous thrombosis, particularly in lower extremity, arterial occlusion, and aneurysm of pulmonary artery and aortic artery **(28).**

VI- Gastrointestinal Involvement:

Gastrointestinal system involvement differs between various populations. The prevalence of gastrointestinal involvement in BD is about 3–60% and it shows regional differences, with approximately 2.8–4.0% in Turkey, India and Saudi Arabia, 10% in China, 38–53% in Japan and 50–60% in the UK. Gastrointestinal symptoms usually start within 4.5–6 years after the onset of oral ulcers. Although mucosal lesions may occur in any part of the digestive track, the ileocecal region is most frequently involved. The most common symptoms are abdominal pain, nausea, vomiting, dyspepsia, diarrhea, and gastrointestinal bleeding. Intestinal BD and Croh's disease (CD) have overlapping characteristics making it hard to distinguish from each other. However, clinical manifestations, endoscopic features, and radiologic characteristics are valuable in differentiating these two conditions **(29).**

VII- Pulmonary Involvement:

Pulmonary involvement is rare in BD (0.7–7%). Pulmonary manifestations have different etiology: embolism, pleurisy, pleural effusion, pulmonary fibrosis (focal or diffuse), infection, vasculitis, The manifestations are mainly related to vasculitis of the pulmonary arteries, veins, and septal capillaries. Pulmonary vascular involvement can lead to aneurysm formation, thrombotic occlusion, hemorrhage, pulmonary infarct **(27).**

VIII- Cardiac Involvement:

Cardiac involvement is accounting for 1 to 6% of patients with BD. The main types of cardiac features are pericarditis, valvular insufficiency, intra cardiac thrombosis and myocardial infarction. Pericardial involvement has been reported as the most common manifestation in some series. Clinical presentation may be acute pericarditis, recurrent pericarditis, constrictive pericarditis, hemorrhagic pericarditis, tamponade or even asymptomatic pericardial effusion **(30).**

IX- Genitourinary System Involvement:

Renal involvement in BD has a rate of 1–4% in different studies but a very small number of BD patients have severe renal insufficiency. Renovascular BD can be divided into two groups according to the type of vessel involvement, macroscopic (medium-sized arteries and veins) and microscopic (small arteries, arterioles, capillaries and venules). Hematuria, proteinuria, leukocyturia and rarely cast may be seen in the patients with renal involvement of BD. Urethritis is not a feature of BD that may facilitate to distinguish it from Reiter's syndrome. Epididymitis and orchitis can also occur in patients with BD, they have a low tendency for recurrence. The attack of epididymitis may be a painless or a painful swelling, but the attack of orchitis, which affects both testicles, is painful. Attacks last for few days or weeks **(31).**

Diagnosis and investigations:

The diagnosis of BD is mainly based on clinical manifestations after ruling out other potential causes. There is no specific laboratory, histopathological, or genetic findings for the diagnosis of BD. Furthermore, there is a large geographical variation both in the disease prevalence and the disease manifestations. Therefore, the diagnosis of BD may be difficult in patients presenting with only major organ involvement such as posterior uveitis, neurologic, vascular, and gastrointestinal manifestations. The emergence of other disease manifestations aiding the definite diagnosis of BD can take months and even years in this group of patients. The disease can also remain limited in some patients, which causes diagnostic difficulty **(32).**

In fact, recent data highlight an increase in the frequency of incomplete BD in Far Eastern, in this group of patients, diagnosis is made according to the presence of specific clinical manifestations of BD by 'expert opinion'. The specific clinical findings such as genital ulcers, ocular, vascular, and parenchymal neurological involvement were proposed to be defined as strong elements for the differential diagnosis of Behçet's disease **(3).**

I-Diagnostic criteria:

The International Study Group ISG criteria, which are the most widely used for diagnosis, were published in 1990, This criteria set was generated by a group of experts following large number of BD patients in daily practice. The presence of oral ulcers. Additionally, two of the following—genital ulceration, eye lesions, skin

lesions, and positive pathergy test—are needed for diagnosis of BD. The main limitation of this criteria set is the exclusion of major organ involvement such as vascular, neurological, and gastrointestinal involvement. Low positivity of the pathergy test, possibly related to less traumatic punctures and changing microbial skin flora **(33).**

In 2014, international criteria for BD (ICBD) were published and included vascular and neurological involvement The ICBD criteria set is based on a scoring system attributing 2 points for oral ulcer, genital ulcer, and ocular lesions; 1 point for positive pathergy test, neurological, and vascular involvement. Patients having ≥4 points are classified as BD **(25).**

The ICBD criteria, which seem more sensitive than ISG criteria but less specific, and in early disease may cause overdiagnosis and patients with spondyloarthropathic features can be mislabeled as BD **(3).**

Recently, an algorithm for the diagnosis of ocular involvement of BD was developed. Superficial retinal infiltrate, signs of occlusive retinal vasculitis, and diffuse retinal capillary leakage, as well as the absence of granulomatous anterior uveitis or choroiditis in patients with vitritis were the items with the highest accuracy in classification and regression tree analysis **(34).**

II-Investigations:

1-Laboratory investigations:

There is no characteristic or pathognomonic laboratory finding in BD. Erythrocyte sedimentation rate and C-reactive protein levels are usually mildly elevated, mainly in cases with arthritis, erythema nodosum-like lesions, or vascular disease. Autoantibodies such as rheumatoid factor, antinuclear, anti-cardiolipin, and anti-neutrophil cytoplasmic antibodies are generally absent. However, it was reported that BD patients with gastrointestinal involvement had higher levels of anti-Saccharomyces cerevisiae antibodies compared to BD patients without gastrointestinal involvement **(33).**

The strongest genetic association was between HLA-B51 and BD, it was shown in different ethnic populations to have positivity ranges around 40–60% in BD. However, HLA-B51 has low diagnostic value for daily practice usage due to its high frequency in the general population in the countries with high BD prevalence **(3).**

There is a significant presence of antiphospholipid antibodies in BD patients compared to controls. Elevated levels of anticardiolipin antibodies (aCL) were observed in 50% of the patients with thrombosis in a group of Iranian patients with BD, Significantly high levels of aCL antibodies were detected in different neurological complications including headache, migraine, dementia, epilepsy and cognitive impairment **(35).**

2-Pathergy test:

The skin pathergy reaction (SPR) is the only diagnostic test currently existing for BD. It is a nonspecific hyperinflammatory response to sterile needle-induced tissue damage, SPR can also be positive in other diseases such as Sweet's syndrome, Crohn's disease, pyoderma gangrenosum, and a few others. Although SPR is quite specific for BD, the sensitivity decreased in the last few decades, possibly due to less traumatic punctures and changing microbial skin flora. A skin histopathology study of pathergy positive and negative patients showed dermal vasculitis indicated by fibrinoid necrosis in pathergy positive (55%) as well as negative patients (39%) **(36).**

3-Imaging:

Imaging may help identify the extent of organ involvement in BD, for diagnosis of ocular, vascular, neurological and cardiac system affection **(3).**

Ocular imaging:

Using enhanced depth optical coherence tomography imaging (EDI–OCT), significantly higher subfoveal choroidal thickness was observed in Behcet uvetitis (BU) patients compared to patients without uveitis, it is a non-invasive method that may be useful for assessing subclinical choroidal involvement**.** OCT-Angiography is a novel imaging technique for the assessment of BD uvetitis, but it still needs enhancement and standardisation in Behçet's uveitis**.** Fluorescein angiography (FA) findings and BD ocular attack score 24 (BOS24) was useful for predicting poor vision in patients with BD **(37).**

Vascular imaging:

Doppler ultrasonography is helpful in diagnosing venous thrombosis and arterial aneurysms in the extremities and in determining whether the thrombosis is acute, subacute or chronic. CT and CT angiography of the chest and abdomen are needed to diagnose larger, proximal vessel involvement. Echocardiography is used for imaging intracardiac thrombosis and transoesophageal echocardiography may be needed to rule out endocarditis **(3).**

Neuroimaging:

Brain stem and/or corticospinal tract syndromes or signs of raised intracranial pressure in a patient with BD often call for a cranial magnetic resonance imaging study with contrast medium and magnetic resonance venography (MRV) to exclude parenchymal or vascular involvement. MRI of the brain with gadolinium contrast agent is the diagnostic imaging method of choice in parenchymal NBD. MR venography (MRV) of the brain as well as MR angiography (MRA) of the brain may be indicated in patients in whom there is clinical suspicion for vascular (venous or arterial) involvement **(38).**

-Neuroelectrophysiological studies:

The electrophysiological tests are an extension of a clinical neurological examination as they help to characterise and localise the lesion, they guide in clinching the pathological diagnosis and thus give prognosis. The commonly used electrophysiological test include Nerve Conduction Studies, Electromyography, Evoked Potentials and Electroencephalography. Nerve conduction studies were used to evaluate peripheral neuropathy involvement in BD patients, and to detect sub clinical affection **(39).**

Treatment

BD typically runs in a relapsing and remitting course, and the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage, A coordinated multidisciplinary approach is necessary for optimal care, treatment choices should be individualized based on age, sex, type, and severity of organ involvement as well as patient preferences. Ocular, vascular, neurological, and gastrointestinal involvement may be associated with a poor prognosis. Given the clinical heterogeneity of BD, the therapeutic approach is highly variable and is guided by the predominant disease manifestation **(40).**

Table 1: Management of Behçet's disease according to European League Against Rheumatism (EULAR) recommendations (40).

Mucocutaneous involvement	• Topical measures such as steroids should be used for the treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer. Papulopustular or acne-like lesions are treated with topical or systemic measures as used in acne vulgaris. • Leg ulcers in BD might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with the help of a dermatologist and vascular surgeon. • Drugs such as azathioprine, thalidomide, interferon-alpha, TNF-alpha inhibitors or apremilast should be considered in selected cases.
Eye involvement	Uveitis of BD requires close collaboration with ophthalmologists with the aim of inducing and maintaining remission. • Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine, cyclosporine-A, interferon alpha or monoclonal anti-TNF antibodies. • Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives.

	• Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon alpha. • Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment. • Isolated anterior uveitis Systemic immunosuppressives could be considered for those with poor prognostic factors such as young age, male sex and early disease onset.
Vascular involvement	➢ Acute deep vein thrombosis • Glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide or cyclosporine-A are recommended. ➢ Refractory venous thrombosis • Monoclonal anti-TNF antibodies could be considered in refractory patients. • Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out. ➢ Arterial involvement • For the management of pulmonary artery aneurysms, high-dose glucocorticoids and cyclophosphamide are recommended. Monoclonal anti-TNF antibodies should be considered in refractory cases. • For patients who have or who are at high risk of major bleeding, embolization should be preferred to open surgery. • For both aortic and peripheral artery aneurysms, medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair. Surgery or stenting should not be delayed if the patient is symptomatic.
Gastrointestinal involvement	• Gastrointestinal involvement of BD should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out. Refractory/severe gastrointestinal involvement • Urgent surgical consultation is necessary in cases of perforation, major bleeding and obstruction. • Glucocorticoids should be considered during acute exacerbations together with disease-modifying agents such as 5-aminosalicylatic acid (5-ASA) or azathioprine. For severe and/or refractory patients, monoclonal anti-TNF antibodies and/or thalidomide should be considered.
Neurological Involvement	• Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering, together with immunosuppressives such as azathioprine. Cyclosporine should be avoided. • Monoclonal anti-TNF antibodies should be considered in severe disease as first-line or in refractory patients. • The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration. • Screening is needed for vascular disease at an extracranial site.

Joint involvement	• Colchicine should be the initial treatment in BD patients with acute arthritis. • Acute monoarticular disease can be treated with intra-articular glucocorticoids. • Azathioprine, interferon-alpha or TNF-alpha inhibitors should be considered in recurrent and chronic cases.

Updates on management of BD:

1-Mucocutaneous involvement:

Apremilast, an orally administered phosphodiesterase-4 inhibitor, has been recently FDA approved for treatment of oral ulcers, shown to be effective for prevention of recurrent oral ulcers, and is a reasonable alternative to colchicine. Apremilast is typically up titrated at a rate of 10 mg daily over six days to achieve a maintenance dose of 30 mg twice daily. Apremilast is associated with improvement in quality of life and some improvement of genital ulcers **(41).**

The efficacy of ustekinumab, an anti IL12/23 antibody was tested in patients with active, treatment-resistant oral and/or genital ulcers. Ustekinumab appeared to be effective in reducing the number and pain of oral ulcers, genital ulcers, skin involvement and articular symptoms **(40).**

2-Ocular involvement:

In patients inadequately controlled with anti-TNF-α agents or IFN-α; here, other new treatments such as IL-1 inhibitors should be considered**.** Several small series have reported success with intravitreal dexamethasone implants for patients with severe or refractory BD uveitis or macular edema **(42).**

3-Vascular involvement:

In refractory arterial involvement Tocilizumab also may be tried **(29).**Several small studies also report improvement with baricitinib**.** There is no consensus for the use of anticoagulant, antiplatelet, or antifibrinolytic agents in vascular BD. A meta-analysis of three retrospective studies showed that immunosuppressives and anticoagulants are superior to anticoagulants alone and adding anticoagulants has no additional benefit **(33).** Anticoagulants seem to be the most effective choice also in case of intracardiac thrombosis. There is limited data suggesting the efficacy of other biological agents such as anakinra, alemtuzumab, and tocilizumab in refractory cases. Tofacitinib was also reported a favorable outcome in patients with BD-related vasculitis **(33).**

3-Gastrointestinal involvement:

Several reports indicate successful treatment of intestinal BD with infliximab and adalimumab using regimens approximating those approved for the treatment of inflammatory bowel disease **(29).**

Alternative options include mycophenolate and methotrexate. Total parenteral nutrition, enteral nutrition, and surgery may be used when clinically indicated **(43).**

4-Neurological involvement:

Other drugs such as IFN-α, methotrexate, mycofenolate mofetile, anti-IL-6 or anti-IL-1 agents may be considered in selected cases as alternative options. Cyclosporine seems to be associated with an increased risk of developing pNBD although the reason is unknown. Cyclosporine should be discontinued or avoided in patients with pNBD **(44).**

5-Joint involvement:

Rare cases necessitating biologics have usually a spondyloarthropathic like course with axial involvement. TNFα inhibitors should be choosen first in these cases. INFα, anti-IL-1 therapies, or secukinumab may be tried in further refractory cases **(33).** Apremilast may also have some benefit for arthritis in patients with arthritis that have not responded to colchicine or other treatments **(45).**

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