



## **Behçet's Disease (BD)**

***Introduction:*** Behçet's Disease (BD) is classified as a form of vasculitis (see "Vasculitis" section) involving both arteries and veins of all sizes. While the most typical signs of BD are oral and genital ulcers, multiple organ systems may be involved. Males and younger patients tend to have more serious disease activity and increased mortality rates. This condition demonstrates a distinct geographic distribution. BD is rare in North America, affecting only 1 in 300,000 individuals. The highest prevalence is found in Turkey, Iran, and Japan, following the ancient "silk route" used by traders. In these populations, BD is perhaps several hundred times more common.

The cause of BD is unknown. Genetic factors are believed to play a role, as the HLA-B51 genetic marker is found in higher frequency among Japanese and Eastern Mediterranean patients. North American, European, and Eastern Indian patients, however, do not demonstrate a specific genetic marker on laboratory testing. Bacterial infections, such as streptococcus, staphylococcus, and *E. coli* have been considered as possible triggers of BD, and viruses such as herpes simplex may also play a causative role. Various immune abnormalities may be found when studying BD patients, including production of proteins known to stimulate the immune system or activate white blood cells. At this time, it is not known whether these abnormalities are inherited or whether they are the response of the immune system to an infection or other exposures that initiate the inflammatory response.

***Features of BD:*** In general, BD demonstrates a pattern of exacerbations and remissions. With the passage of time, the overall disease activity tends to diminish. Most patients present with oral and/or genital ulcers. Ocular (eye) and central nervous system involvement may develop several years after the initial diagnosis. While mortality rates are low for patients exhibiting only oral and skin involvement, loss of vision is a significant risk in patients with ocular BD. A higher mortality risk is associated with involvement of the central nervous system, gastrointestinal tract, or other major organ systems.

Essentially 100% of all patients with BD will develop recurrent mouth sores, known as *aphthous ulcerations*. Mucous membrane (mouth) lesions consist of painful, shallow ulcers that occur on the inner lips, tongue, cheeks, and gum line. They tend to heal without scarring in ~ 2 or 3 weeks. These ulcers are often indistinguishable from canker sores. Genital ulcers occur in approximately 80% of BD patients. Typical

locations for these lesions are on the scrotum and penis in males and on the vulva or vagina in women. As opposed to the oral ulcers, these lesions tend to result in permanent scarring after healing but do not recur as frequently.

Cutaneous (skin) lesions exhibit a variety of different presentations. They may appear as red painful nodules resembling *erythema nodosum*, large and painful ulcers with ragged borders known as *pyoderma gangrenosum*, or flat red and inflamed regions resembling *Sweet's syndrome*. In other patients, small vessel cutaneous vasculitis may occur, giving rise to *purpura* (see "Vasculitis" section). Still others may demonstrate pustular and acne-like lesions, particularly in the "beard" area in men. A curious finding, mostly in Middle Eastern patients with BD, is known as *pathergy*. This phenomenon is characterized as an intense inflammatory response in the skin after minor injury such as blood drawing. While an uncommon finding in North American patients, when present pathergy is quite suggestive of BD.

Eye involvement in BD may occur in either the anterior (front) or posterior (back) sections (or "chambers") of the eye. *Uveitis* or *iritis*, inflammation of the iris in the anterior chamber of the eye, and *hypopyon*, pus in the anterior chamber, are common findings in those with ocular complications. While these conditions present with more dramatic symptoms of redness, blurring, and pain in the affected eye, more commonly patients experience painless blurring in one or both eyes and note "spots" in their visual field. For this reason, it is important for BD patients to have regular eye examinations by an ophthalmologist to prevent progressive vision loss and even blindness which may occur as complications of this disease.

Arthritis in BD is usually inflammatory and nonerosive (causing no joint damage). Often, only 1 to 3 joints are involved, either in a symmetric or asymmetric distribution. Joints most commonly involved include the knees, wrists, ankles, and elbows. Arthritis symptoms generally last a few weeks at a time and then resolve.

Central nervous system (CNS) involvement generally includes the lower part of the brain known as the *brainstem* and the connections between the brain and spinal cord. Patients may present with balance problems, weakness on one side, or less commonly of all four limbs. Non-infectious inflammation around the lining of the brain (*meningitis*) may result in headaches or behavioral problems. Patients with progressive CNS involvement tend to have a poor prognosis.

Pulmonary (lung) manifestations in BD may include *aneurysms* in the pulmonary artery, *pulmonary hypertension* (elevated pressures in the lung circulation), blood clots (*emboli*) in the lungs, and scarring of lung tissue. Rarely, a connection between an artery and the lung known as a *fistula* develops and presents as sudden coughing up of large amounts of blood. This severe complication requires immediate recognition and treatment. Cardiac manifestations can include heart attacks and inflammation surrounding the lining of the heart (*pericarditis*).

Vascular (blood vessel) complications include inflammation and clotting of veins (*phlebitis*), which can involve small veins on the surface of the skin or deeper veins as large as the inferior vena cava in the center of the body. Aneurysms or swelling around the arteries known as *pseudo-aneurysms* may develop, sometimes merely after puncturing the artery with a needle for blood drawing.

Ulcerations may occur in the gastrointestinal tract, most often in the region where the small intestine joins the colon. These patients may present with abdominal pain, bleeding, or perforation of the bowel. This latter complication requires prompt surgical intervention to remove the involved area of intestine. Kidney involvement is uncommon in BD, with inflammation of the kidney (*nephritis*) or protein deposits in the kidney (*amyloidosis*) being the major features. Amyloidosis typically develops when treatment of chronic inflammation is less than optimal.

***Diagnosis:*** Because of the variable course of BD, most patients exhibiting a pattern of exacerbations and remissions, health care providers may require several months to make the correct diagnosis. There are no laboratory tests or x-ray findings that reliably diagnose BD, although nonspecific findings on such studies may aid in the evaluation of the patient and help rule out other conditions such as systemic lupus erythematosus (see related section). The diagnosis of BD rests upon the history of the illness and findings on physical examination of the patient.

Criteria for diagnosing BD were devised in 1990 by an international committee and include:

1. Recurrent oral ulceration, *plus* 2 of the following:
2. Recurrent genital ulceration
3. Eye lesions
4. Skin lesions
5. Positive “pathergy test”

The pathergy test consists of stimulating an area of previously normal skin with a needle and observing the inflammatory response described above in the “*Features of BD*” section. This test has much more reliability in Middle Eastern populations, where pathergy is a much more common finding. Occasionally, biopsies of affected areas or dye studies of arteries or veins may assist health care providers in the diagnosis of BD, but for the most part any other investigations only supplement the criteria listed above.

***Therapy:*** (See “Medications” section for further details) The broad spectrum of findings in BD makes management of this condition quite challenging. Depending on the symptom presentation of BD, various specialists may need to be involved in treating the patient, including regular eye exams, as mentioned above, to prevent potential permanent visual loss.

Milder mucous membrane and cutaneous lesions, including oral and genital ulcers, can be treated with *topical steroid preparations*, *non-steroidal anti-inflammatory drugs* (NSAIDs) such as *ibuprofen* (Motrin) or *naproxen* (Naprosyn), *anti-histamines* such as *diphenhydramine* (Benadryl), *colchicine*, and *dapsone*. Colchicine, a medication also commonly used for the treatment, may reduce the frequency and/or severity of oral and genital lesions. Diarrhea, nausea, and rare occurrence of suppression of white blood cell counts at higher doses are the major side effects of colchicine. Dapsone, a medication originally designed for the treatment of leprosy, may be quite useful in the treatment of skin lesions as well as oral or genital ulcers. Patients starting dapsone should be screened for deficiency of an enzyme known as G6PD before starting therapy,

as such individuals experience destruction of red blood cells when receiving this drug. Most patients, however, have few serious side effects to these medications.

More serious mucocutaneous lesions that are unresponsive to the above therapies may require the use of *thalidomide*, *methotrexate* (MTX), and/or a low dose of *prednisone* or other corticosteroid preparations. Thalidomide, a medication that is available only by special request in the United States, was taken off the market years ago due to the occurrence of severe birth defects in children born to mothers taking this drug. Men or women without child-bearing potential are the best candidates to receive thalidomide. Mild nerve damage is the other major side effect of thalidomide that requires routine monitoring. The side effects of MTX include suppression of the immune system, elevation of liver enzymes, and lowering of white blood cell counts. As discussed in other sections, cortico-steroid medications have a wide array of side effects including weight gain, loss of bone strength/density, elevation of blood sugar levels, cataracts, and suppression of the immune system that must be factored in before initiating therapy for a given patient.

Patients with disease involving major organs such as the eyes, heart, lungs, or CNS require more intensive immunosuppressive therapy. Steroids may be given alone or in combination with other agents, and may need to be started at higher doses for more severe disease. Other immunosuppressive medications utilized may include *azathioprine* (Imuran), *cyclosporine* (Neoral), *cyclophosphamide* (Cytosan), and *chlorambucil* (Leukeran). All of these drugs have the potential to make patients prone to infection and lower the blood counts. Azathioprine may additionally cause elevation of liver enzymes, while cyclosporine may impair kidney function, and cyclophosphamide can cause irritation of and occasionally bleeding in the bladder if not given with adequate fluids.

*Interferon- $\alpha$*  (Roferon) is an injectable medication with anti-viral effects that has a role in treating certain patients with BD. This medication does not suppress the immune system substantially but modifies the inflammatory response. Fever or flu-like symptoms and a lowering of the seizure threshold are among the side effects of interferon- $\alpha$ . Recently, *tumor necrosis factor* (TNF) *antagonists* such as *etanercept* (Enbrel), *infliximab* (Remicade), and *adalimumab* (Humira) that are used in treating rheumatoid arthritis have been utilized for treating BD, and initial results are encouraging.

Specific treatment recommendations vary depending on the patient's individual symptoms and findings. Therapy generally requires supervision by a physician familiar with the various treatment options and their unique risk/benefit profiles. Long-term prognosis for BD patients is generally good as long as the disease is recognized promptly and treated appropriately.