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# Behçet's syndrome

## A bird's eye review of the recent literature

*edited by Vedat Hamuryudan and Hasan Yazıcı*

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### Reviews

**Authors:** Krause I, Weinberger A.

**Title:** Behçet's disease.

*Curr Op Rheumatol* 2008; 20: 82-7.

**Summary:** A comprehensive review with special emphasis on the recent developments in the epidemiology, genetics, pathogenesis and treatment of Behçet's syndrome (BS).

**Authors:** Mumcu G, Inanc N, Yavuz S, Direskeneli H.

**Title:** The role of infectious agents in the pathogenesis, clinical manifestations and treatment strategies in Behçet's disease.

*Clin Exp Rheumatol* 2007; (Suppl. 45): S27-S34.

**Summary:** An infectious etiology was claimed even by Hulusi Behçet at his first paper describing BS. Although still a dilemma, there is growing information indicating the involvement of microbial agents and microbial antigens in the etiology, clinical manifestations and treatment of BS. This comprehensive review helps us to better understand the relationships between infectious agents and immune mechanisms in BS.

### Epidemiology

**Authors:** Houman MH, Neffati H, Braham A, Harzallah O, Khanfir M, Miled M, Hamzaoui K.

**Title:** Behçet's disease in Tunisia. Demographic, clinical and genetic aspects in 260 patients.

*Clin Exp Rheumatol* 2007; (Suppl. 45): S58-S64.

**Summary:** This retrospective study reports the various features of 260 Tunisian BS patients (188 men) who had been registered at a tertiary referral center over a 20-year period (1987-2006). The diagnosis of BS was made according to the international classification criteria. In general, many features of the patients were similar to series reported from other countries. HLA B51 positivity was 54% among patients and 25.5% among healthy controls. The frequency of pathergy positivity was 62%. One fifth of the patients had irreversible visual impairment at presentation. The frequency of gastrointestinal involvement (1.5%) was low. Sixty-three patients had central nervous system involvement (CNS) with the majority (75%) having parenchymal type. Interestingly, 13 patients (21%) had both parenchymal and cerebral vascular involvement, which is usually not expected to occur in the same patient. Erythema nodosum and arthritis were more frequent among women while pseudofolliculitis and deep vein thrombosis predominated among men.

### Pathology

**Author:** Hirohata S.

**Title:** Histopathology of central nervous system lesions in Behçet's disease

*J Neurol Sciences* 2008; 267: 41-7.

**Summary:** CNS involvement is one of the leading causes of mortality and morbidity in patients with BS. There is a paucity of histopathologic studies, which sometimes also failed to demonstrate true vasculitis. This paper summarizes the immunohistopathological findings of brain tissues obtained from 3 patients who had different stages of CNS involvement. Irrespective of the clinical stage, the predominating lesion was perivascular cuffing of T lymphocytes and monocytes infiltrating the small vessels. There were scattered areas of neurons undergoing apoptosis with the formation of a few binucleated neurons. The autopsy tissue of a patient with long standing CNS disease revealed atrophy of basal pons with formation of cystic or moth-eaten lesions, consisting of isomorphic gliosis with viable neurons.

**Authors:** Lee I, Park S, Hwang I, Kim MJ, Nah SS, Yoo B, Song JK.

**Title:** Cardiac Behçet disease presenting as aortic valvulitis/aortitis or right heart inflammatory mass: A clinicopathologic study of 12 cases.

*Am J Surg Pathol* 2008; 32: 390-8.

**Summary:** This paper again brings up the interesting issue of the variable clinical expression of BS at different geographies. Eight of the 12 patients with cardiac involvement had aortic valve regurgitation which is rarely observed in patients from the Middle Eastern or Mediterranean countries. It was also interesting that none of the 12 patients had venous thrombosis, which frequently accompanies cardiac involvement in patients from Middle Eastern or Mediterranean origin. Echocardiographic examination of some patients with aortic regurgitation revealed formation of conglomerated mass or echo free space extending into aortic root or interventricular septum suggesting periaortic abscess. Paravalvular leakage within 1 year after surgery necessitating revision surgery developed in 4 patients when only aortic valve replacement without the resection of aorta was performed. This complication did not occur when the surgical procedure was changed to aortic root resection, composite graft reconstruction and extensive debridement along with immunosuppressive treatment. Both the right heart and left heart lesions showed similar histopathological features consisting of endothelial damage, mixed type inflammation, microabscess formation with granulomatous reaction, fibrin deposits and fibrosis.

## Pathogenesis

**Authors:** Lew W, Chang JY, Jung JY, Bang D.

**Title:** Increased expression of interleukin-23 p19 mRNA in erythema nodosum-like lesions of Behçet's disease.

*Br J Dermatol* 2008; 158: 505-11.

**Summary:** IL-23 is a newly discovered cytokine which is composed of a p19 subunit and a shared p40 subunit of IL12. In this study skin biopsies from the erythema nodosum like lesions of BS patients and skin biopsies of psoriatic patients and healthy controls were examined. Elevated levels of IL-23 p19 mRNA were found in BS patients and psoriasis patients. However, there were no significant differences in IL-12 and IL23 serum levels of BS patients and healthy controls. These findings suggest that the expression of IL-23 p19 mRNA may be associated with development of erythema nodosum like lesions in BS patients.

**Authors:** Turan B, Pfister K, Diener PA, Hell M, Möller B, Boyvat A, Ergin S, Villiger PM.

**Title:** Soluble tumour necrosis factor receptors sTNFR1 and sTNFR2 are produced at sites of inflammation and are markers of arthritis activity in Behçet's disease.

*Scand J Rheumatol* 2008; 37: 135-41.

**Summary:** This prospective study found higher plasma sTNFR1 and sTNFR2 levels in BS patients with active disease and especially with active arthritis. Also tissue samples of mucocutaneous lesions showed a strong staining for TNFR2 and mast cells were identified as the major source for this receptor. These results underline the fundamental role of TNF/TNFR pathway in BS.

**Authors:** Do JE, Kwon SY, Park S, Lee ES.

**Title:** Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behçet's disease.

*Rheumatology (Oxford)* 2008; 47: 840-8.

**Summary:** This study showed that the monocytes of patients with active BS show higher expression of toll-like receptor (TLR) 2 and TLR4 than those of patients with psoriasis and healthy controls. 25(OH)D levels were inversely correlated with the expressions of TLR2, TLR4 and activity indicators. In vitro, treatment of monocytes with 25(OH)D showed a dose dependent suppression of the protein and mRNA expressions of TLR2 and TLR4. TNF alpha synthesis decreased with TLR ligand stimulation in Vitamin D treated monocytes. These results point to the importance of TLR2 and TLR4 triggered inflammation in the pathogenesis of BS.

## Clinical aspects

**Authors:** Seyahi E, Ugurlu S, Cumali R, Balci H, Ozdemir O, Melikoglu M, Hatemi G, Fresko I, Hamuryudan V, Yurdakul S, Yazici H.

**Title:** Atherosclerosis in Behçet's syndrome

*Semin Arthritis Rheum* 2008 an 24 [epub ahead of print]

**Summary:** Many indirect observations, like the paucity of coronary artery disease and ischemic cerebrovascular events, suggest that BS is not associated with increased atherosclerosis. This study formally evaluated the presence of subclinical atherosclerosis among 239 BS patients with varying degrees of disease severity by using B-mode ultrasonography, a validated tool for measuring intima media thickness and detecting atherosclerotic plaques. Patients with rheumatoid arthritis and ankylosing spondylitis and apparently healthy volunteers of the hospital staff were studied as controls. The frequency of atherosclerotic plaques in the carotid and femoral arteries were similar between patients with BS, ankylosing spondylitis and healthy controls but was increased significantly in men with rheumatoid arthritis even after adjustment of atherosclerotic risk factors. The mean intima media thickness was similar between patients with BS and control groups. The type of organ involvement in BS did not show an influence on the ultrasonographic indices.

**Authors:** Hatemi G, Fresko I, Tascilar K, Yazici H.

**Title:** Increased entesopathy among Behçet's syndrome patients with acne and arthritis.

*Arthritis Rheum* 2008; 58: 1539-45.

**Summary:** A previous study showed that the arthritis of BS co-exists with acne like lesions. This study, by using ultrasonography, found significantly more entesopathy among BS patients having acne and arthritis. Bony component of entesopathy (erosions and / or enthesophyte) was present in 40% of BS patients with acne and arthritis, in 18% of BS patients with no arthritis, in 54% of patients with ankylosing spondylitis, in 28% of patients with rheumatoid arthritis and in 16% of healthy controls. These results support the hypothesis that BS patients with acne and arthritis form a distinct cluster carrying features of spondyloarthropathies.

**Authors:** Tugal-Tutkun I, Cingü K, Kir N, Yeniad B, Urgançoglu M, Gül A.

**Title:** Use of laser flare-cell photometry to quantify intraocular inflammation in patients with Behçet uveitis.

*Graefes Arch Clin Exp Ophthalmol* 2008; 246: 1169-77.

**Summary:** Laser flare-cell photometry (LFCP) is an automated and noninvasive method that quantifies anterior segment inflammation by measuring protein content and cells in the anterior chamber. This study assessed the usefulness of LFCP in quantifying intraocular inflammation in the uveitis of BS. The study groups consisted of BS patients with no ocular involvement, BS patients with uveitis either during attacks or in remission and healthy controls. Masked measurements with LFCP were compared with scores obtained from clinical assessment. Mean flare was not increased in patients without uveitis but it was significantly higher in patients with uveitis both during attacks and in remission. Significant correlations were found between the scores and clinical condition of the uveitis. The use of this technique seems to be promising not only in obtaining quantitative data in clinical trials but also in reducing the need for fluorescein angiography for patients who are in remission.

**Authors:** Haghighi AB, Aflaki E, Ketabchi L.

**Title:** The prevalence and characteristics of different types of headache in patients with Behçet's disease, a case control study.

*Headache* 2008; 48: 424-9.

**Summary:** In this case control study, 180 BS patients of a referral center and 1023 healthy hospital workers were evaluated for the presence and different types of headache. All subjects filled in a questionnaire and those reporting headache were examined by a single neurologist. Headache was reported by 65% of the patients. Migraine type headache was the most frequent form and was found in 27% of BS patients compared to 11% of the controls. The frequency of tension type headache was not different from that of the controls (24% vs. 20%). In 8% of the patients headache was part of the clinical spectrum of neurological involvement. Ocular involvement was the cause of headache in 3% of the patients.

**Authors:** Akpolat T, Dilek M, Aksu K, Keser G, Toprak Ö, Cirit M, Oguz Y, Taskapan H, Adibelli Z, Akar H, Tokgoz B, Arici M, Celiker M, Diri B, Akpolat I.

**Title:** Renal Behçet's disease: An update

*Semin Arthritis Rheum* 2008 [epub ahead of print]

**Summary:** Renal involvement is relatively rare in BS. It may have a wide spectrum ranging from asymptomatic proteinuria and hematuria, to glomerulonephritis, amyloidosis, renal vascular involvement and treatment related toxicity leading to end stage renal failure. This comprehensive review is an update of a previous report that was published in 2002. The authors report a total of 253 BS patients with various types of renal involvement including their 33 patients. Amyloidosis was the leading cause of renal involvement followed by glomerulonephritis and renal vascular disease. Clinical and histopathological findings, approach to the diagnosis and treatment are discussed in detail.

## Therapy

**Authors:** Ahn JK, Lee YS, Jeon CH, Koh EM, Cha HS.

**Title:** Treatment of venous thrombosis associated with Behçet's disease: immunosuppressive therapy alone versus immunosuppressive therapy plus anticoagulation.

*Clin Rheumatol* 2008; 27: 201-5.

**Summary:** The treatment of venous thrombosis is one of the most challenging and controversial issues in BS. This retrospective study reports 37 BS patients (32 men) with venous thrombosis who have received either immunosuppressives alone (n=16), a combination of immunosuppressives and anticoagulants (n=17) or anticoagulants alone (n=4). Patients with isolated superficial thrombosis were excluded. Recurrence of venous thrombosis occurred in 2 (12.5%) patients receiving immunosuppressives alone, in 1 (5.9%) patient receiving combination therapy and in 3 (75%) of the 4 patients receiving anticoagulants alone. The results of this small study again suggest that vessel wall inflammation rather than

a hypercoagulable state is operative in the development of venous thrombosis of BS and underline the need of prospective and larger studies.

**Authors:** Elezoglu A, Kafasi N, Kaklamanis PH, Theodossiadis PG, Kapsimali V, Choremi E, Vaipoulos G, Sfrikakis PP.

**Title:** Infliximab treatment-induced formation of autoantibodies is common in Behçet's disease.

*Clin Exp Rheumatol* 2007; (Suppl. 45): S65-S69

**Summary:** BS in general is not associated with any specific autoantibody production. This prospective study assessed the production of autoantibodies in 20 BS patients who received infliximab treatment for at least 6 months and compared the findings with those of 35 matched patients who had not received infliximab. At baseline, only 1 patient from either group had low titers of antinuclear antibodies. However after 6 months of infliximab treatment 65% of the patients had antinuclear antibodies. Although not present at baseline, the formation of anti-dsDNA antibodies of IgM isotype was detected in 35% of patients after 6 months of infliximab treatment. Similarly, 6 of 20 treated patients but none of the control patients had developed low to moderate titers of anti  $\beta$ 2GPI-IgM antibodies at month 6. In general, the titers of autoantibodies tended to rise with continued infliximab treatment but remained in low titers or even disappeared after the discontinuation of infliximab. None of the patients tested positive for anti-ENA, ANCA, RF or anti-CCP either at baseline or under treatment and no patient developed any clinical symptoms that might be associated with the development of autoantibodies. The results of this study suggest that the production of autoantibodies under infliximab treatment is independent from the underlying disease.

**Authors:** Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain MA, Gül A, Houman MH, Kötter I, Olivieri I, Salvarani C, Sfrikakis PP, Siva A, Stanford MR, Stübiger N, Yurdakul S, Yazici H.

**Title:** EULAR recommendations for the management of Behçet's disease: Report of a task force of the European standing committee for international clinical studies including therapeutics (ESCISIT)

*Ann Rheum Dis* 2008; [epub ahead of print]

**Summary:** This is a report of 9 recommendations on the management of different aspects of BS that have been developed by a multidisciplinary expert committee. These recommendations were formed by combining the best available published evidence with the opinion of the experts by using Delphi method. Recommendations on the eye, skin-mucosa disease and arthritis are mostly evidence based while those on vascular, neurological and gastrointestinal involvements largely rely on expert opinion and uncontrolled evidence.

**Authors:** Kobayashi K, Ueno F, Bito S, Iwao Y, Fukushima T, Hiwatashi N, Igarashi M, Iizuka BE, Matsuda T, Matsui T, Matsumoto T, Sugita A, Takeno M, Hibi T.

**Title:** Development of consensus statements for the diagnosis

and management of intestinal Behçet's disease using a modified delphi approach.

*J Gastroenterol* 2007; 42: 737-45.

**Summary:** Gastrointestinal involvement is probably the best example for the geographical variability of BS in disease expression. It is frequent in Japan and Far Eastern countries but rare in other parts of the world. This paper summarizes practice guidelines for diagnosis and treatment of gastrointestinal involvement in BS. These recommendations were developed following a literature search and by collecting the responses of the gastroenterology specialists to hypothetical case scenarios with the use of a modified Delphi method.

**Authors:** Pipitone N, Olivieri I, Padula A, D'Angelo S, Nigro A, Zuccoli G, Boiardi L, Salvarani C.

**Title:** Infliximab for the treatment of neuro-Behçet's disease: A case series and review of the literature

*Arthritis Rheum* 2008; 59: 285-90.

**Summary:** This paper reports 8 BS patients with CNS involvement who were treated with infliximab. According to the experience of the authors, infliximab appears to be a promising agent for remission induction and possibly for the maintenance treatment of CNS involvement. The paper also summarizes 4 additional patients who were reported before in the literature with similar responses to infliximab.