Behçet's syndrome.
A bird's eye review of the recent literature

edited by Vedat Hamuryudan and Hasan Yazici

Reviews

Authors: Calamia KT, Schirmer M, Melikoglu M.
Title: Major vessel involvement in Behçet disease.
Curr Opin Rheumatol 2005;17: 1-8.

Authors: Hamuryudan V, Öz B, Tüzün H, Yazici H.
Title: The menacing pulmonary artery aneurysms of Behçet's syndrome.
Clin Exp Rheumatol 2004; 22 (Suppl 34) S1-3.

Authors: Borhani-Haghighi A, Pourmand R, Nikseresht AR.
Title: Neuro-Behçet disease. Areview.
Neurologist 2005;11: 80-9.

Epidemiology

Authors: Cakir N, Dervis E, Benian O, Pamuk ON, Sonmezates N, Rahimoglu R, Tuna S, Cetin T, Sarikaya Y.
Title: Prevalence of Behçet's disease in rural Western Turkey: Apreliminary report.
Clin Exp Rheumatol 2004; 22 (Suppl 34): S53-5.
Summary: This is a field survey from a rural area in Thrace (European Turkey) near Greece and Bulgaria. The authors screened 4861 inhabitants for Behçet's syndrome (BS) and found only 1 patient having oral ulcers, folliculitis and a positive pathergy test. The 2: 10000 point prevalence rate for BS found in this study was lower than that had been reported in 4 former studies performed in different parts of Turkey. The authors suggest that the different ethnical make-up of the study population might account for this low prevalence.

Authors: Pipitone N, Boiardi L, Olivieri I, Cantini F, Salvi F, Malatesta R, La Corte R, Triolo G, Ferrante A, Filippini D, Paolazzi G, Sarzi-Puttini P, Restuccia G, Salvarani C.
Title: Clinical manifestations of Behçet's disease in 137 Italian patients: results of a multicenter study.
Clin Exp Rheumatol 2004; 22 (Suppl 36): S46-51.
Summary: This is a retrospective survey of 137 patients from 9 different referral centers in Italy. The clinical characteristics of the Italian patients are not different from those reported from other geographies.

Pathogenesis

Authors: Mahesh SP, Li Z, Buggage R, Mor F, Cohen IR, Chew EY, Nussenblatt RB.
Title: Alpha tropomyosin as a self-antigen in patients with Behçet's disease.
Clin Exp Immunol 2005; 140: 368-75.
Summary: It has previously been reported by Mor F *et al*. (*Eur J Immunol*, 2002) that alpha tropomyosin might be a self antigen in Behçet's. The current study takes this further and shows that 6/18 patients with BD demonstrate lymphoproliferative responses against alpha tropomyosin in vitro which is significantly higher than that observed among healthy controls and patients with non-infectious uveitis.

Authors: Ureten K, Ertenli I, Ozturk MA, Kiraz S, Onat AM, Tuncer M, Okur H, Akdogan A, Calguneri M.
Title: Neutrophil CD64 expression in Behçet's disease.
J Rheumatol 2005; 32: 849-52.
Summary: CD64 expression in neutrophils is upregulated in response to microbial agents and certain proinflammatory cytokines. The authors investigated neutrophil CD64 expression in Behçet patients with active or inactive disease along with diseased and healthy controls. CD 64 expression among inactive patients was found to be similar to that in healthy controls but was significantly increased in patients with active disease. However, this increase was less than that observed in controls with active infection and similar to that in patients with other inflammatory diseases.

Authors: Inanc N, Mumcu G, Birtas E, Elbir Y, Yavuz S, Ergun T, Fresko I, Direskeneli H.
Title: Serum mannose-binding lectin levels are decreased in Behçet's disease and associated with disease severity.
J Rheumatol 2005; 32: 287-91.
Summary: As an indicator of dysregulation in innate immunity low serum mannose binding lectin (MBL) levels have been implicated in the pathogenesis of some autoimmune diseases. This study showed that serum MBLlevels were significantly lower in Behçet patients compared to those observed in healthy controls but not different from those among patients with recurrent oral ulceration. There was also an inverse correlation between disease severity and serum MBL levels which necessitates a closer look at innate immunity in this condition

Authors: Amoura Z, Dode C, Hue S, Caillat-Zucman S, Bahram S, Delpech M, Grateau G, Wechsler B, Piette JC.
Title: Association of the R92Q TNFRSF1Amutation and extracranial deep vein thrombosis in patients with Behçet's disease.
Arthritis Rheum 2005; 52: 608-11.
Summary: In this study 5 of the 74 (6.8%) unrelated European Behçet patients had heterozygous R92Q TNF receptor superfamily 1A mutation compared to 1.3% of 909 healthy controls (p=0.006). On the other hand only 1 of the 38 Maghrebian patients (i.e. patients from Morocco, Algeria, Tunisia) had this mutation but none of the 89 Maghrebian con-

trols. All 6 (5 European and 1 Maghrebian) patients with R92Q TNFRS1Amutation had extracranial deep vein thrombosis. This association was significant after correction for multiple comparisons. The study provides further evidence for the polygenic nature of Behçet`s syndrome.

Authors: Duymaz–Tozkir J, Yilmaz V, Uyar FA, Hajeer AH, Saruhan–Direskeneli G, Gul A.
Title: Polymorphisms of the IL-8 and CXCR2 genes are not associated with Behçet's disease.
J Rheumatol 2005; 32: 93-7.
Summary: This is a polymorphism study looking at some potentially important mutations however with negative results.

Authors: Alpsoy E, Elpek GO, Yilmaz F, Ciftcioglu MA, Akman A, Uzun S, Karakuzu A.
Title: Androgen receptor levels of oral and genital ulcers and skin pathergy test in patients with Behçet's disease.
Dermatology 2005; 210: 31-5.
Summary: This study examined androgen receptor levels in biopsy samples of oral ulcers, genital ulcers and skin pathergy test areas in BS patients. Normal appearing and adjacent skin–mucosa areas of the same patients served as controls. Androgen receptor levels in biopsy samples of skin pathergy test were significantly higher compared to normal appearing control tissue. The levels were also higher in men compared to women. The androgen receptor levels of oral ulcers and genital ulcers were not different from those of control areas. The authors interpreted their findings as another clue showing the importance of androgens in the pathogenesis of BS.

Authors: Hatemi G, Bahar H, Uysal S, Mat C, Gogus F, Masatlioglu S, Altas K, Yazici H.
Title: The pustular skin lesions in Behçet's syndrome are not sterile.
Ann Rheum Dis 2004; 63: 1450-2.
Summary: Previous contention was that pustular lesions of Behçet's syndrome were sterile, but this study shows that these lesions are infected. Comparison of their microbiology with those of acne vulgaris patients showed that *S. aureus* was significantly more common in pustules of Behçet's syndrome patients. Whether these lesions are secondarily infected, and whether these microorganisms play a role in the pathogenesis remains to be seen.

Clinical aspects

Authors: Uzun O, Akpolat T, Erkan L.
Title: Pulmonary vasculitis in Behçet disease: a cumulative analysis.
Chest 2005; 127: 2243 - 53.
Summary: This is a comprehensive literature review about pulmonary involvement in BS. Pulmonary artery aneurysms are the most common reported pulmonary complication of BS with more than 200 cases reported until May 2003. This excellent review summarizes the clinical characteristics, diagnostic problems, available therapies and prognosis of patients with pulmonary involvement.

Authors: Erkan D, YaziciY, Sanders A, Trost D, Yazici H.
Title: Is Hughes-Stovin syndrome Behçet's disease?
Clin Exp Rheumatol 2004; 22: S64-8.
Summary: The coexistence of pulmonary artery aneurysm and systemic thrombosis is called as Hughes-Stovin syndrome (HSS) when additional clinical manifestations suggestive BS or other inflammatory disorders are absent. Based on a case report this paper describes the similarities between HSS and BS and finally comes to the conclusion that HSS is in fact BS.

Authors: Saip S, Siva A, Altintas A, Kiyat A, Seyahi E, Hamuryudan V, Yazici H.
Title: Headache in Behçet's Syndrome.
Headache 2005; 45: 911-9.
Summary: This prospective study on 228 randomly chosen BS patients attending a multidisciplinary referral center revealed the presence of headache in 151 (66%). Headache was primary in 58% of patients. Twenty-four percent of the patients reported tension type headache and 15% reported migraine. A paroxysmal predominantly frontal migrainous headache was also reported in 18% of the patients. In 5% of the patients headache was associated with neurological involvement and in 4% with eye inflammation. These results suggest that headache is the most common neurological symptom of BS occurring both in patients with or without neurological involvement.

Authors: Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M.
Title: Uveitis in Behçet disease: an analysis of 880 patients.
Am J Ophthalmol 2004; 138: 373-80.
Summary: This was a retrospective study among a large number of patients followed in a large eye clinic in Turkey during 2 decades. The study is in line with previous observations that uveitis in men has a more severe course compared to women. Also, confirming previous studies the rate of visual loss was lower after 1990 most probably as a result of the more aggressive immunosuppressive treatment.

Authors: Gedik S, Akova Y, Yilmaz G, Bozbeyoglu S.
Title: Indocyanine green and fundus fluorescein angiographic findings in patients with active ocular Behçet's disease.
Ocul Immunol Inflamm 2005; 13: 51-8.
Summary: Fluoresceine fundus angiography (FFA) is a useful diagnostic tool for vasculitic ocular changes but choroidal circulation is assessed better with indocyanine green angiography (ICG). In this study ICG and FFA were performed in the same session in 49 eyes of 25 patients with BS. Optic disc hyperfluorescence was the most common finding on both FFA and ICG. The authors conclude that FFA and ICG complement each other as diagnostic tools as ICG detected some findings not seen by FFA. However, since these findings were not specific or pathognomic the authors do not recommend performing either procedure in routine practice.

Authors: Seyahi E, Memisoglu E, Hamuryudan V, Tepe S, Aker UT, Balci H, Ongen Z, Yurdakul S, Yazici H.

Title: Coronary atherosclerosis in Behçet's syndrome: a pilot study using electron-beam computed tomography.
Rheumatology (Oxford). 2004; 43: 1448-50.
Summary: This study investigated the frequency of coronary atherosclerosis in BS with electron beam computerized tomography. All patients were male and were selected specifically for the presence of major vessel involvement and a long disease duration. Abnormal findings suggesting coronary atherosclerosis was found in only 3 of 24 (12%) study patients suggesting that coronary atherosclerosis is low in BS even in a group of patients selected to represent worst disease conditions.

Authors: Leiba M, Seligsohn U, Sidi Y, Harats D, Sela BA, Griffin JH, Livneh A, Rosenberg N, Gelernter I, Gur H, Ehrenfeld M.
Title: Thrombophilic factors are not the leading cause of thrombosis in Behçet's disease.
Ann Rheum Dis 2004; 63: 1445-9.
Summary: This study found no differences between BS patients with and without thrombophlebitis in the levels of a list of thrombophilic factors and gene polymorphisms commonly associated with thrpmbophilia. On the other hand dyslipidemia manifested mainly as hypertrigliceridemia appeared to be a risk factor for thrombosis.

Authors: Tunc R, Saip S, Siva A, Yazici H.
Title: Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome.
Ann Rheum Dis 2004; 63: 1693-4.
Summary: A previous study from Israel had shown that CNS involvement in Behçet's was associated with peripheral vessel disease (Krause I *et al*. Clin Exp Rheumatol, 1999). Parenchymal involvement and dural sinus thrombosis are the two main types of central nervous system (CNS) involvement in BS. The current study showed that it is the dural sinus thrombosis moeity of CNS disease that is actually associated with vascular involvement elsewhere in the body. Patients with parenchymal involvement do not show such an association.

Treatment

Authors: Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, Hamuryudan V, Yazici H.
Title: Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study.
J Rheumatol 2005; 32: 98-105.
Summary: This is the first controlled study with an anti TNF agent in BS. Forty men with BS, all having positive skin pathergy and monosodium urate tests and also having active mucocutaneous symptoms and/or arthritis were randomized to receive either etanercept 25 mg two times a week or placebo for 4 weeks. While treatment with etanercept did not, interestingly, affect the pathergy or the monosodium urate tests during the trial, etanercept was significantly effective in suppressing most of the mucocutaneous symptoms as well as the acute phase responses when compared to placebo.

Authors: Sfikakis PP, Kaklamanis PH, Elezoglu A, Katsilambros N, Theodossiadis PG, Papaefthimiou S, Markomichelakis M.
Title: Infliximab for recurrent sight threatening ocular inflammation in Adamantiades–Behçet disease.
Ann Intern Med 2004; 140: 404-6.
Summary: This letter reports an open study among 25 Behçet patients with severe eye disease in whom infliximab was administered at a dose of 5 mg/kg at the immediate onset of uveitis in addition to their ongoing immunosuppressive treatment. The response was rapid; complete response of vitritis and retinitis was achieved at day 7 in 68%. All patients became complete responders at day 28. Fifteen patients with more refractory eye disease were enrolled in a 32 week protocol with multiple infliximab infusions. Complete response was eventually reached at 9/16 of these patients, as well. The results of this study underlines the need to urgently compare the effect of TNF alpha antagonists with more traditional agents like cyclosporin A in formal controlled clinical trials in eye disease asscoiated with Behçet's.

Authors: Lindstedt EW; Baarsma GS, Kuijpers RW, van Hagen PM.
Title: Anti-TNF-alpha therapy for sight threatening uveitis.
Br J Ophthalmol 2005; 89: 533-6.
Summary: An observational study on the use of infliximab in 13 patients with serious sight threatening treatment resistant uveitis of whom 6 had BS. Infliximab was given at a dose of 3 mg/kg and the infusion was repeated only when clinically needed. Ocular inflammatory signs diminished in less than 7 days to 3 weeks following infusion whereas improvement in visual acuity started within a few days. Remission was accomplished in most patients following 1 – 3 infusions and they could be subsequently managed with conventional immunosuppressives during follow up for at least 2 years.

Authors: Wechsler B, Sable-Fourtassou R, Bodaghi B, Huong DL, Cassoux N, Badelon I, Fain O, LeHoang P, Piette JC.
Title: Infliximab in refractory uveitis due to Behçet's disease.
Clin Exp Rheumatol 2004; 22: S14-6.
Summary: This is a report of 4 patients treated with infliximab 5 mg/kg because of severe uveitis resistant to other drugs. Infliximab was found to be effective in all patients.

Authors: Hamuryudan V, Er T, Seyahi E, Akman C, Tüzün H, Fresko I, Yurdakul S, Numan F, Yazici H.
Title: Pulmonary artery aneurysms in Behçet's syndrome.
Am J Med 2004; 117: 867-70.
Summary: Ten years ago we had reported that half of 24 patients with pulmonary artery aneurysms had died within 1 year after the onset of haemoptysis However, most patients in this study had been diagnosed in the early 1980's, when the experience about this complication was rather limited. This retrospective study re-evaluated the outcome of pulmonary aneurysms in a more recent cohort. The 5 year survival rate among 26 patients was 62% and this was signifi-

cantly better than what we had reported earlier. It is most likely that the improvement in the outcome was the result of earlier recognition and treatment of this complication.

Authors: Iscan ZH, Vural KM, Bayazit M.
Title: Compelling nature of arterial manifestations in Behçet disease.
J Vasc Surg 2005; 41: 53-8.
Summary: This paper, from a large vascular surgery center in Turkey, described its experience on surgical treatment for arterial complications of BS. Between 1990 and 2003, 20 patients (17 being men) had 34 vascular operations. The most common type arterial manifestation was the abdominal aortic aneurysm. The authors used synthetic and avoided autologous venous grafts.
The 10 year mortality rate (including operative mortality) was 70% and the 10 year complication free survival rate was 13%. Unfortunately the article did not give information about the post-surgical immunosuppressive treatment during the follow-up.

Familial Mediterranean fever. A bird's eye review of the recent literature

edited by E. Ben-Chetrit

Pathogenesis

Authors: Diaz A, Hu C, Kastner DL, Schaner P, Reginato AM, Richards N, Gumucio DL.
Title: Lipopolysaccharide-induced expression of multiple alternatively spliced MEFV transcripts in human synovial fibroblasts: a prominent splice isoform lacks the C-terminal domain that is highly mutated in familial Mediterranean fever.
Arthritis Rheum 2004; 50: 3679-89.
Summary: The objective of this study was to investigate expression of the familial Mediterranean fever (FMF) gene (MEFV) in human synovial fibroblasts, chondrocytes, and peripheral blood leukocytes (PBLs). The subcellular localization of pyrin, the MEFV product, was determined in transfected synovial fibroblasts and HeLa cells with plasmids encoding pyrin isoforms. MEFV was expressed in synovial fibroblasts, but not in chondrocytes. Consensus and alternatively spliced transcripts were induced by lipopolysaccharide in synovial fibroblasts and PBLs. In transfected cells, the proteins encoded by all highly expressed splice forms were cytoplasmic. In contrast, native pyrin was predominantly nuclear in synovial fibroblasts, neutrophils, and dendritic cells, but was cytoplasmic in monocytes. The authors conclude that several MEFV transcripts are expressed and inducible in synovial fibroblasts. While recombinant forms of all major pyrin isoforms are cytoplasmic, native pyrin is nuclear in several cell types. This study confirms previous findings of Matzner's group in Jerusalem regarding the expression of MEFV gene in fibroblasts.

Genetics and phenotype–genotype correlations

Authors: Aldea A, Calafell F, Arostegui JI, Lao O, Rius J, Plaza S, Maso M, Vives J, Buades J, Yague J.
Title: The West Side Story: MEFVhaplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination "hot-spot" at the MEFV locus.
Hum Mutat 2004; 23: 399.
Summary: In this paper the authors analyzed intragenic MEFVSNPs in Spanish and Chueta (descendants of converted Jews) FMF patients and controls. They showed that there is a strong linkage disequilibrium (LD) at the MEFVlocus and an intragenic recombination hot spot. They also found that the MEFV mutation spectrum in Spain is quite diverse and similar to those of France and Italy. However, the Chueta spectrum was poorer and closer to that of North African Jews, suggesting a direct connection with the Jewish diaspora.
Authors: Topaloglu R, Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, Bakkaloglu A.
Title: E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever.
Ann Rheum Dis 2005; 64: 750-2. E-pub 2004 Sept. 30.
Summary: The objective of this study was to evaluate the phenotypic features of patients with the E148Q mutation. The subjects included 26 patients who were homozygous for E148Q, 10 who were compound heterozygous for E148Q, and 8 complex cases. The results showed that although 4 of the 26 patients with E148Q/E148Q were asymptomatic at the time of evaluation, abdominal pain was present in 77% of the patients, fever in 66%, arthralgia in 50%, arthritis in 15.4%, and vomiting in 23.8%. None of the patients had amyloidosis, but 2 with E148Q/E148Q had a family history of amyloidosis and one had rapidly progressive glomerulonephritis secondary to vasculitis, which progressed to chronic renal failure. The authors conclude that patients homozygous for E148Q have a heterogeneous clinical presentation. Most are symptomatic and colchicine treatment is required in these patients. Yet the authors do not explain why 4 out of 26 E148Q homozygotes were asymptomatic. This fact suggests that an additional factor is needed in order to express the disease.