Behçet's Syndrome
A bird's eye review of the recent literature

edited by Vedat Hamuryudan and Hasan Yazıcı

Epidemiology

Authors: Liozon E, Roussin C, Puéchal X, Garou A, Valadier P, Périnet I, Raffray L, Théry Y, De Lagarde B.
Title: Behçet's disease in East African patients may not be unusual and is an HLA-B51 negative condition: A case series from Mayotte (Comoros).
Joint Bone Spine. 2010 Jul 2. [Epub ahead of print]
Summary: BS is only sporadically reported from Africa. This may reflect the rarity of this condition among African people but may also be due to under-diagnosis. This retrospective study describes the clinical characteristics of 14 BS (10 males) patients who have been diagnosed and followed-up in an East-African country. The mean disease duration was 5.5 years at the time of diagnosis, reflecting the difficulties in diagnosing BS. The frequencies of orogenital ulcers (100%) and cutaneous manifestations (64%) were similar to those reported from other countries. However, central nervous system involvement (39%), vascular involvement (31%), gastrointestinal involvement (10%) and arthritis (79%) were more frequent while eye disease was less (15%). This report, taken together with the results of a recent population-based study from France, that reported a higher prevalence of BS among North-African populations compared to native Europeans (Mahr A *et al*. *Arthritis Rheum* 2008), further underlines the presence of BS in Africa.

Authors: Klein P, Weinberger A, Altmann VJ, Halabi S, Fachereldeen S, Krause I.
Title: Prevalence of Behçet's disease among adult patients consulting three major clinics in a Druze town in Israel.
Clin Rheumatol 2010;
Summary: A high prevalence of BS among Druze population had already been reported by the same group before. However, this study relied only on those patients who had already received a diagnosis of BS. This time, the authors screened all patients who visited one of the three largest clinics in a town in Israel that has more than 95% Druze population. First, patients having recurrent oral ulcers were identified and then they were interviewed and examined for the presence of BS. Patients having at least one additional BS symptom underwent pathergy testing. Among 1083 patients visiting the clinics during a period of 6 months there were 63 patients (5.8%) with a diagnosis of recurrent oral ulceration. Further examination of these patients led to the diagnosis of BS in 2 patients which gave a prevalence of 50–185:100.000. This high figure places the Druze population among those with the highest prevalence of BS in the world. Since the Druze community is almost genetically isolated (traditions encourage marriage within the same geographical area and prohibit marriage with persons from other religions) studies on genetic and environmental factors specific to this community may help to further understand the pathogenesis of BS.

Authors: Ertam I, Kitapcioglu G, Aksu K, Keser G, Ozaksar A, Elbi H, Unal I, Alper S.
Title: Quality of life and its relation with disease severity in Behçet's disease.
Clin Exp Rheumatol 2009; 27 (2 Suppl 53): s18-22.
Summary: Data on the level of quality of life of BS patients and its relation with disease severity are limited. This cross-sectional study evaluated the quality of life in 195 BS patients being followed in the outpatient clinics of a tertiary referral centre. The results showed that the quality of life of BS patients, assessed by SF-36 and WHOQOL-100 scores, were lower than those of healthy controls. General health and vitality domains of SF-36 and physical health, psychological, level of independence, social relations, environment and environmental public domains of WHOQOL were significantly lower in patients with active disease. Arthritis, eye involvement and vascular involvement were the main clinical features significantly affecting the quality of life of the patients. Despite a rightful statement at the introduction of the manuscript saying that any systemic disease having a considerable morbidity and mortality may influence the quality of life of the affected patients, this study did not include diseased controls.

Pathogenesis

Authors: Kappen JH, Wallace GR, Stolk L, Rivadeneira F, Uitterlinden AG, van Daele PL, Laman JD, Kuijpers RW, Baarsma GS, Stanford MR, Fortune F, Madanat W, van Hagen PM, van Laar JA.
Title: Low prevalence of NOD2 SNPs in Behçet's disease suggests protective association in Caucasians.
Rheumatology (Oxford) 2009; 48: 1375-7.
Summary: BS and Crohn's disease have many similar clinical features suggesting similar etiopathogenesis. The aim of this study was to assess the frequency of three NOD2 variants that have been shown to be associated with Crohn's disease among Caucasian and Middle Eastern BS patients and healthy controls. Contrary to what had been expected, Arg702Trg and Leu1007fs were found to be significantly lower among BS patients than healthy controls whereas the frequency of Gly908Arg variant was similar between groups. In the subgroup analysis, only the Arg702Trg variant was found to be significantly reduced among Caucasian patients indicating to a possible protective role for developing BS

in this population. The addition of a diseased control group consisting of Crohn's patients would have made the interpretation of this study more meaningful.

Authors: de Menthon M, Lavalley MP, Maldini C, Guillevin L, Mahr A.
Title: HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies.
Arthritis Rheum 2009; 15: 1287-96.
Summary: Although the association of HLAB51/B5 with BS is a well-known issue, the risk increase shows a wide variation ranging between1.6 and 16 across different ethnicities. This meta-analysis, which included 78 case-control studies with a total of 4800 patients and 16289 controls, found a pooled OR of 5.78 (95%CI: 5.00–6.67) for BS susceptibility among HLAB51/B5 carriers. The subgroup analyses of studies among populations of different ethnicities gave similar ORs with overlapping 95%CIs. The results of this study once again underline that HLAB51/B5 is the strongest genetic marker for the susceptibility to BS in all ethnic goups.

Authors: Touma Z, Farra C, Hamdan A, Shamseddeen W, Uthman I, Hourani H, Arayssi T.
Title: TNF polymorphisms in patients with Behçet disease: a meta-analysis.
Arch Med Res 2010;41:142-6.
Summary: This meta-analysis of 10 studies from different ethnic populations found a weak but significant increased risk of BS with -1031C and -238A alleles and a significant decreased risk of BS with -857T allele.

Clinical aspects

Authors: Kaburaki T, Araki F, Takamato M, Okinaga K, Yoshida A, Numaga J, Fujino Y, Kawashima Y.
Title: Best-corrected visual acuity and frequency of ocular attacks during the initial 10 years in patients with Behçet's disease.
Graefes Arch Clin Exp Ophthalmol 2010; 248: 709-14.
Summary: This retrospective study, looking at the clinical outcome of ocular involvement in BS, includes 39 patients who had been seen in an ophthalmology centre within 1 year after the first ocular attack and had a follow-up of more than 10 years. Colchicine (n = 37), cyclosporine A (n= 26) and prednisolone (n=26) were the most frequently used drugs. 7 patients received only one agent (colchicine n=5, cyclosporine A n= 2) while the others received more than one drug during their follow-ups. Although the results suggested better visual outcomes compared to earlier reports the mean best corrected visual acuity continued to deteriorate and was less than 0.1 in 39% of the affected eyes at 10 years. The decrease in visual acuity was more pronounced during the first 3 years. The number of ocular attacks also tended to decrease with time but still nearly half of the patients were developing ocular attacks at 10 years. Macular and chorioretinal atrophy were the main reasons of poor visual outcome. It is important to note that still an undue reliance on colchicine had been made in patient management in this series. Formal implementation research related to management is surely needed in BS.

Authors: Chung MJ, Cheon JH, Kim SU, Park JJ, Kim TI, Kim NK, Kim WH.
Title: Response rates to medical treatments and long-term clinical outcomes of nonsurgical patients with intestinal Behçet's disease.
J Clin Gastroenterol 2010; 44: e116-22.
Summary: This is a retrospective study of 93 BS patients who had initially received medical treatment after being diagnosed as having intestinal involvement in a university clinic in Korea during a period of 15 years. The mean follow-up of the patients was 77 months. Remission rate at week 8 was 67% after initiation of treatment that consisted mainly of mesalazine (99% of the patients), colchicine (37%), corticosteroids (28%) and azathioprine (5%). The recurrence rates requiring surgery were 6.7% at 2 years and 15% at 5 years. Failure to achieve remission at week 8, the presence of deep and volcano shape ulcers, and the presence of gastrointestinal symptoms at the time of diagnosis were factors predicting recurrence.

Authors: Ahn JK, Oh JM, Lee J, Koh EM, Cha HS.
Title: Behçet's disease associated with malignancy in Korea: a single center experience.
Rheumatol Int 2010; 30: 831-5.
Summary: The occurrence of malignant diseases among BS patients has not been adequately studied. In this retrospective study the authors evaluated the medical charts of 1769 BS patients registered in a tertiary referral centre. 72 BS patients with no malignant disease served as controls. There were 32 BS patients (1.8%) having malignant disease. In the majority (69%) the diagnosis of malignant disease was made during follow-up of the patients for BS. However, in 10 patients (31%) malignancy was diagnosed either concomitantly or before the diagnosis of BS. Seven patients had a history of immunosuppressive use (azathioprine or cyclosporine A) but the frequency of immunosuppressive use was not different from that of a control group. Twenty patients (62.5%) had solid tumors and 12 (37.5%) had haematologic malignancy. Myelodysplastic disease (7 patients) and thyroid cancer (4 patients) were the most common malignant diseases. The disease characteristics of the patients with malignancy were not different from those of the control group. However, intestinal involvement was significantly more frequent among patients with haematologic malignancy than those with solid cancer.

Authors: Hirohata S, Kikuchi H.
Title: Histopathology of the ruptured pulmonary artery aneurysm in a patient with Behçet's disease.
Clin Exp Rheumatol 2009; 27 (2 Suppl 53): s91-5.
Summary: This paper describes the detailed post-mortem findings in a patient who died as a result of ruptured pulmo-

nary artery aneurysm (PAA). The ruptured aneurysm showed thrombus formation and recanalisation along with proliferation of small vessels and perivascular infiltrating mononuclear cells leading to disruption of the elastic fibers in the vascular wall. Perivascular monuclear cells in the thrombus mainly consisted of CD45RO+ T cells and CD68+ monocytes and few CD20+ B cells. The ruptured proportion of the aneurysm lacked lamina elastica indicating to pseudoaneurysm. These findings suggest that thrombus formation and recanalisation are the primary events in the development of PAA.

Prognosis

Authors: Hamuryudan V, Hatemi G, Tascilar K, Sut N, Ozyazgan Y, Seyahi E, Mat C, Yurdakul S, Yazici H.
Title: Prognosis of Behçet'syndrome among men with mucocutaneous involvement at disease onset: long term outcome of patients enrolled in a controlled trial.
Rheumatology (Oxford) 2010; 49: 173-7.
Summary: It is known that BS runs a more severe course among men. This study addressed the question whether being major organ involvement free during the initial years of their disease course is indicating to a better prognosis at the long term for men with BS. For this purpose the authors evaluated 91 men with BS who had been enrolled in a double blind, placebo controlled trial of thalidomide 11.7 years before. None of the patients had clinically significant major organ involvement at the time of the entrance to the trial. However, 39 patients (43%) had developed major organ involvement necessitating immunosuppressive treatment during their follow-up after the trial. Eye disease and vascular involvement were the most frequent indications for the use of immunosuppressives. The development of major organ involvement was significantly more frequent among patients developing BS at younger age than those developing at older age. The results also suggested a possible effect of colchicine in reducing the need of immunosuppressive use among patients with older age at onset, which warrants further studies. The results of this study suggest that men developing BS at young age are still at increased risk for a more severe outcome even if they have no major organ involvement during the initial years of their disease.

Authors: Saadoun C, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, Cacoub P.
Title: Mortality in Behçet's Disease.
Arthritis Rheum 2010 May 23. [Epub ahead of print]
Summary: This retrospective study found 5% mortality among 817 BS patients during a median follow-up of 7.7 years in a single centre in France. The mortality among patients of non-European origin was higher (5.7) than that of European origin (4.1%) but this did not reach statistical significance. The mortality rate was higher among young patients and tended to decrease with increasing age. Major vascular involvement, malignity and central nervous system involvement were the main causes of mortality. Male sex, arterial involvement and higher number of BS flares were associated with mortality. These results are generally in line with previous observations.

Treatment

Authors: Deuter CME, Zierhut M, Möhle A, Vonthein R, Stübiger N, Kötter I.
Title: Long term remissions after cessation of interferon alpha treatment in patients with severe uveitis due to Behçet's disease.
Arthritis Rheum 2010 Jun 1. [Epub ahead of print]
Summary: This is a retrospective study assessing the efficacy of IFN-alpha among 53 BS patients with severe uveitis and a minimum follow-up period of 2 years. The response to IFN was high with 52 (98%) of the patients achieving remission allowing to stop treatment in 47 (89%) patients. Re-institution of treatment was required in 20 (43%) of these patients 17 in whom IFN was again used. The response to second course was also satisfactory and IFN could be stopped in 11 patients (65%). A third course was needed only in 4 patients. The estimated remission rates after stopping IFN were 75% at 19 months, 50% at 46 months and 25% at 107 months. Women tended to have lower relapse rates than men. Ethnicity and HLA-B51 had no influence on the response to treatment. Although there are no controlled studies, IFN seems to provide long-term drug-free remissions in BS patients with severe uveitis which has not been seen with other drugs including TNF alpha inhibitors.

Authors: Ciancio G, Colina M, La Corte R, Lo Monaco A, De Leonardis F, Trotta F, Govoni M.
Title: Nicotine-patch therapy on mucocutaneous lesions of Behçet's disease: a case series.
Rheumatology (Oxford) 2010;49:501-4.
Summary: This paper reports an anectodal experience with nicotine patch therapy in 5 BS patients (4 men) who developed the first symptom of BS after cessating smoking. Mucocutaneous manifestations regressed in 4 patients during the 6 months observation period but they recurred within 1 month after stopping patch-therapy. One patient, failing to respond to nicotine patches, re-started smoking and reported regression of oral and genital ulcers within a few days. However, other systemic manifestations of BS (arthritis and uveitis) did not respond to nicotine patch therapy.