
Behçet's Syndrome

A bird's eye review of the recent literature

edited by Vedat Hamuryudan and Hasan Yazici

Genetics

Authors: Mizuki N, Meguro A, Ota M, Ohno S, Shiota T, Kawagoe T, Ito N, Kera J, Okada E, Yatsu K, Song YW, Lee EB, Kitaichi N, Namba K, Horie Y, Takeno M, Sugita S, Mochizuki M, Bahram S, Ishigatsubo Y, Inoko H.

Title: Genome-wide association studies identify *IL-23R* – *IL-12RB2* and *IL-10* as Behçet's disease susceptibility loci. *Nat Genet* 2010; 42: 703-7.

Summary: This genome-wide association study with large number of Japanese BS patients and unaffected controls identified two suggestive new association loci on chromosomes 1p31.3 and 1q32.1, which include interleukin-10 and interleukin receptor genes *IL-23*, *IL-12*. The authors then made a meta-analysis by combining the results from additional Turkish and Korean cohorts which also confirmed these associations. *IL-10* is an anti-inflammatory cytokine and a functional defect in this cytokine might at least partly explain the propensity for inflammation, the hallmark of BS. On the other hand, the association with mutations in the *IL-23* gene brings us back to the old debate BS being part of the seronegative spondylarthritides. Future studies looking at perhaps quantitative alterations in these cytokines will help us to better understand the complex pathogenesis of BS.

Authors: Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C, Le JM, Yang B, Korman BD, Cakiris A, Aglar O, Emrence Z, Azakli H, Ustek D, Tugal-Tutkun I, Akman-Demir G, Chen W, Amos CI, Dizon MB, Akdag-Kose A, Azizlerli G, Erer B, Brand OJ, Kaklamani VG, Kaklamani P, Ben-Chetir E, Stanford M, Fortune F, Ghabra M, Ollier WER, Cho YH, Bang D, O'Shea J, Wallace GR, Gadina M, Kastner DL, Gül A.

Title: Genome-wide association study identifies variants in the MHC class I, *IL-10*, and *IL-23-IL-12RB2* regions associated with Behçet's disease. *Nat Genet* 2010; 42: 698-702.

Summary: This genome-wide association study with 311,459 single nucleotide polymorphisms (SNP) in 1215 patients with BS and 1278 healthy controls from Turkey found the most significant associations on chromosome 6 in the MHC region. Occurrence of the HLAB*51 variant was present in 59% of the BS patients and 29% of the controls. The most significantly associated SNPs associated within this region were located in the area encoding MHC class I chain related sequence A (MICA). Additionally, an association at *IL-10* was identified. A meta-analysis using additional cohorts from Turkey, the Middle East, Europe and Asia showed associations at *IL-10* and *IL-23R* locus. Also note our comments for the previous article.

Authors: Jiang Z, Yang P, Hou S, Du L, Xie L, Zhou H, Kijlstra A.

Title: *IL-23R* gene confers susceptibility to Behçet's disease in a Chinese Han population.

Ann Rheum Dis 2010; 69: 1325-8.

Summary: Recent studies have found a strong association between the *IL-23R* gene and several diseases like rheumatoid arthritis, ankylosing spondylitis and Crohn's disease. The authors of this study had previously identified a BS-related SNP located in the *IL-23R* gene. This time they studied the association of four SNPs of the *IL-23R* gene with BS in a population of Chinese Han BS patients and healthy controls. They have found a strong association with a SNP, rs17375018 in the *IL-23R* gene with uveitis in BS. The results also suggest a possible protective role of the AGCG haplotype against uveitis in this population. Also note our comments for the previous 2 articles.

Authors: Masatlioglu S, Seyahi E, Turanli ET, Fresko I, Gogus F, Senates E, Savran OF, Yazici H.

Title: A twin study in Behçet's syndrome.

Clin Exp Rheumatol 2010; 28 (Suppl. 60): S62-S66.

Summary: This study looked at the monozygotic and dizygotic twin-sibling frequency and disease concordance rate in BS. The study groups consisted of 1705 consecutive BS patients attending a dedicated clinic and 7761 healthy university students. Initially, a questionnaire was used to identify those with twin siblings. Those with positive answers were invited to the clinic for interviews and laboratory tests to confirm the twin-ship. The frequency of having a twin-sibling was lower among BS patients (0.82%) compared to controls (1.55%; $p=0.022$). Six of the 14 BS patients (43%) and 28 of the 120 controls (23%) had a monozygotic twin. Two of the 6 (0.33; 95%CI: -0.21–0.88) monozygotic twins and 1 of the 8 (0.13; 95%CI: -0.17–0.42) dizygotic twins had concordant pairs for BS. The frequency of monozygotic twin births was not different from the healthy population in Turkey. Even though the number of twins studied was small – still the largest twin study in BS – the persistence of discordance (4/6) at 8 years is salutable evidence for environmental factors in BS.

Epidemiology

Authors: Seyahi E, Turanli ET, Mangan MS, Celikyapi G, Oktay V, Cevirgen D, Kuzuoglu D, Ozoglu S, Yazici H.

Title: The prevalence of Behçet's syndrome, familial Mediterranean fever, HLA B51 and *MEFV* gene mutations among ethnic Armenians living in Istanbul, Turkey.

Clin Exp Rheumatol 2010; 28 (Suppl. 60): S67-S75.

Summary: Disease frequencies in closed ethnic communities may help to understand the influence of genetic and environmental factors in disease pathogenesis. This study looked for the frequencies of BS and FMF among the Armenian population living in Istanbul. In the first part of the study, the parents of the Armenian primary school students were surveyed with questionnaires whether they have been diagnosed as having BS or FMF. Those with a positive response were invited for interviews. Tests for HLAB51 and *MEFV* mutations were also done in Armenian and non-Armenian volunteers. The study found a lower frequency of BS (90 per 10⁵) among the Armenians compared to that found in the general population of Istanbul suggesting a genetic predisposition for BS. Interestingly, the frequency of HLAB51 was similar between Armenian and non-Armenian population pointing to the possible presence of yet unknown genetic factor(s) in the development of BS. The study also showed a higher prevalence of FMF among Armenians (760 per 10⁵) compared to the general population. The carrier rate of *MEFV* gene mutations was similarly higher in Armenians (36%) compared to controls (20%; $p=0.015$) suggesting a higher genetic load for FMF, a condition called Armenian disease in this geography before.

Registries

Authors: Kone-Pait I, Darce-Bello M, Shahram F, Gattorno M, Cimaz R, Ozen S, Cantarini L, Tugal-Tutkun I, Assaad Khalil S, Hofer M, Kuemmerle-Deschner J, Banamour S, Al Mayouf S, Pajot C, Anton J, Faye A, Bono W, Nielsen S, Letierce A, Tran TA, PED-BD International Expert Committee.

Title: Registries in rheumatological and musculoskeletal conditions. Paediatric Behçet's disease: an international cohort study of 110 patients. One-year follow-up data. *Rheumatology* (Oxford) 2011; 50: 184-8.

Summary: This study reports one-year data of a multinational cohort of 110 paediatric patients suspected to have BS. To be included in the cohort, patients younger than 16 years had to have a clinical suspicion of BS defined as the mandatory presence of recurrent oral ulceration and at least one BS related symptom or a documented positive family history. At inclusion 38% of the patients had one symptom in addition to recurrent oral ulceration, 31% had 2 additional symptoms and 31% had 3 or more additional symptoms. A positive family history was present in 20% of the patients reflecting the strong genetic component of pediatric BS. During one-year follow-up one-third of these patients developed at least one new symptom and the diagnosis of BS was confirmed in 30 of 48 (62%) evaluated patients. Genital ulcers and skin lesions were significantly associated with the classification for definite BS. The study is on going with the ultimate aim to set-up an algorithm for the definition of BS in children.

Clinical aspects

Authors: Ideguchi H, Suda A, Takeno M, Ueda A, Ohno S, Ishigatsubo Y.

Title: Behçet's disease: evolution of clinical manifestations. *Medicine* (Baltimore) 2011; 90: 125-32.

Summary: This is an interesting study looking at the chronologic appearance and the cumulative evolution of individual manifestations of BS patients at the long-term. The study group consisted of 412 BS patients (228 women, 184 men) who were followed up in 2 university hospitals in Japan during a period of 16.5 years. Recurrent oral ulceration was the most common initial symptom (in 70% of the patients), followed by skin lesions (24%), genital ulcers (16%) and eye involvement (14%). Most (78%) of the patients reported a single symptom at the onset whereas 22% reported the simultaneous occurrence of 2 or more symptoms. Initial appearance of oral ulcers preceded the diagnosis of BS for a mean of 7.5 years. However, the appearance of skin lesions, genital ulcers and eye involvement occurred more near in time (less than 2 years) to the diagnosis of BS. On the other hand, the more serious manifestations such as CNS, GI and vascular involvement tended to develop later in the course of BS. Male sex and HLAB51 were more frequent among patients with eye involvement, whereas females had more frequent genital ulceration and arthritis. The frequency of eye involvement was higher in those with CNS involvement and lower in those with GI and vascular involvement. The development of serious organ involvement could not be predicted from the combination of initial major symptoms (oral ulcers, genital ulcers, skin lesions and eye involvement). A decrease in the rate of complete BS according to the Japanese Criteria at the time of diagnosis (having all four major symptoms listed above) was found among patients diagnosed more recently compared to those diagnosed earlier. Despite its retrospective design, this important study highlights important data on the development and course of BS.

Authors: Riera-Mestre A, Martinez-Yelamos S, Martinez-Yelamos A, Ferrer I, Pujol R, Vidaller A.

Title: Clinicopathologic features and outcomes of neuro-Behçet's disease in Spain: A study of 20 patients. *European J Int Med* 2010; 21: 536-41.

Summary: This retrospective study describes 20 BS patients with neurologic involvement who had been admitted to a tertiary centre during a period of 20 years. 80% of the patients had parenchymal involvement. The onset of neurologic involvement was acute, with symptoms appearing suddenly and evolving over several days. Fever, headache, mostly unilateral motor weakness and cranial nerve palsy were the most common clinical symptoms at admission. During a mean of 6.3 years (range: 0.5–20) follow-up, 12 (60%) patients experienced a total of 22 relapses. At the end of follow-up, 7 (35%) patients had a poor outcome including 4 deaths. This study also reports histological findings of 4 patients including one post-mortem examination. The histopathological findings were similar in all the biopsies and included perivascular

lymphocytic infiltration, presence of macrophages, reactive astrocytosis and microgliosis. The autopsy case had focal necrosis of variable sizes in the region of lateral ventricle, internal capsule, left striatum nucleus and in the right thalamus. Interestingly, there was no endothelial degeneration or other signs of vasculitis, suggesting that neuro-BS might be the result of a perivascular inflammatory process rather being a true vasculitis.

Treatment

Authors: Onal S, Kazokoglu H, Koc A, Akman M, Bavbek T, Direskeneli H, Yavuz S.

Title: Long term efficacy and safety of low dose and dose escalating interferon alfa 2a therapy in refractory Behçet uveitis.

Arch Ophthalmol 2011; 129: 288-94.

Summary: Although there are no formal studies, interferon alfa is regarded as an effective and rapid acting agent in the treatment of severe posterior uveitis of BS and this is also emphasised in EULAR recommendations. However, the ideal dose and duration of interferon treatment are not established. Higher dosages (6 MU daily) of interferon appear to be more effective than lower dosages its adverse effects are also dose related. This open study reports the efficacy of low dose interferon alfa 2a in the treatment of sight threatening and severe uveitis in 37 BS patients who were refractory to at least one conventional immunosuppressive agent. Initially, interferon was given daily at a dose of 3 MU for 14 days followed by a maintenance dose of 3 MU 3 times a week. In case of relapse, the dose of interferon alfa was gradually increased up to 9 MU 3 times per week. This regimen appeared to be effective in suppressing the rate of uveitis relapses, in discontinuing concomitant steroid treatment and achieving drug free remissions. This protocol has the advantage of a

lower cost and avoids important side effects of higher dose regimens.

Authors: Marcomichelakis N, Delicha E, Masselos S, Fariadaki K, Kaklamanis P, Sfrikakis P.

Title: A single infliximab infusion vs. corticosteroids for acute panuveitis attacks in Behçet's disease: a comparative 4-week study.

Rheumatology (Oxford) 2011; 50: 593-7.

Summary: This is an open, non-randomised study comparing the short-term efficacy of a single infusion of infliximab (5 mg/kg) with that of high dose methylprednisolone (1g/day intravenously for 3 days) or intra-vitrear triamcinolone acetate (4 mg) in the treatment of acute panuveitis occurring in 35 eyes of 22 BS patients. All 3 treatments were similarly effective on visual acuity at 4 weeks. However, compared with corticosteroids, infliximab suppressed the ocular inflammation scores significantly faster and more effectively. The authors concluded that a single infusion of infliximab should be always considered for the control of acute panuveitis of BS.

Authors: Kose O, Simsek I, Pay S.

Title: Mycophenolate sodium in the treatment of mucocutaneous Behçet's disease.

Int J Dermatol 2011; 50: 895-6.

Summary: A previous uncontrolled study was stopped prematurely when the interim analysis on the first 6 patients showed inefficacy of mycophenatemofetil in the treatment of the mucocutaneous lesions of BS (Adler YD *et al.*, *Dermatology* 2001; 203: 322-4). The current study is also an open-labelled, uncontrolled trial suggesting that enteric coated mycophenolate sodium might be effective in controlling the mucocutaneous lesions of 10 BS patients during a period of 6 months. Given the fact that mycophenolate sodium exerted similar efficacy to what is usually seen with azathioprine, these findings emphasise the need for controlled studies.