

Meeting report

Highlights of the 10th International Congress on Behçet's Disease

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Introduction

The 10th International Conference on Behçet's Disease was held in the Free University of Berlin during June 27-29, 2002 under the auspices of the International Society for Behçet's Disease. 167 physicians participated in the meeting during which around 200 abstracts were presented.

Epidemiology

The papers on epidemiology were mainly based on hospital registries except for one field survey from Iraq that reported a disease prevalence of 17/100,000 (1). There was a decrease in the number of patients in an ophthalmology department in Japan (2) and in Iran (3) with a trend towards milder forms of the disease especially in Iran. A higher familial occurrence was reported among the ethnic Turkish patients in the German Registry compared to the native Germans (18% vs 4.5%) (4). An abstract from Israel said that patients with a late (> 40 years) disease onset had similar clinical characteristics when compared to those with younger onset (5).

Clinical findings

The problem of complex aphthosis defined as frequent oral aphthae and genital ulcers unrelated to Behçet's disease was addressed and the need for a more rigorous differential diagnosis of such conditions especially in areas with a low prevalence of the disease was emphasized (6). 3.8% of the patients followed up because of recurrent aphthous stomatitis developed Behçet's disease in Turkey, a figure which was far lower than was previously reported by Bang from Korea (52%) (7). Pathergy was positive in only 20% of the patients who turned out to have Behçet's disease and the main factor that seemed to make a difference was the presence of early onset disease with large ulcerations. Smoking decreased the number of oral ulcers in two studies although

the reasons underlying it were not clear (8,9). Ultraviolet radiation was applied to the forearm of the patients with Behçet's disease and the minimal erythematous dose was found to be lower in patients compared to controls in spite of the potential bias due to complexion (10). This was proposed as another example of non-specific immune reactivity in Behçet's that could be used for research purposes. It was emphasized that it was not a diagnostic test.

Several neurological case series affirmed that parenchymal central nervous system disease had a worse prognosis than sagittal sinus thrombosis and that inflammatory cerebrospinal fluid findings constituted one of the most important prognostic factors (11, 12). The occasional spinal involvement was also related to a bad prognosis (13) and it was demonstrated that 4.5% of the cases of a cohort of patients with neurological involvement experienced seizures in the form of tonic clonic convulsions especially at times of neurological activation (14). The infrequent coexistence of parenchymal central nervous system disease and sagittal sinus thrombi was further underlined (15).

A grading system for ocular inflammation was proposed and it was suggested that posterior pole inflammation was nearly always involved in cases where the retina could not be visualized due to severe anterior segment inflammation (16). The value of optical coherence tomography in the quantification of macular edema was also studied (17).

Disease activity and prognosis

Reports on the chronology of clinical manifestations from Iran, Turkey and Japan claimed that new episodes of neurological, gastrointestinal and large vessel involvement could be observed late in the course of the disease compared to other manifestations that usually abate with the passage of time (18-20). The highest mortality and the most

severe forms of the disease were encountered in the young male in all series with major vessel disease being the most important risk factor (19, 21, 22). Of a cohort of patients with Behçet's disease 3.25% were reported to develop lymphoid and hematological malignancies in Ankara Turkey (23).

A dichotomous scoring system improved the validity of the Behçet's Disease Activity Index (BDAI, Leeds) but there were still differences in the interpretation of major vessel and eye disease among various countries; a factor that hampers the international use of the instrument (24). A local disease activity index was developed by the Koreans that attempted to overcome the cultural differences (25). A study from Turkey revealed that the IBD-DAM scoring systems and BDAI were comparable (26) and another study showed that the addition of psychometric probes to BDAI would provide additional and valuable information (27). An important argument that was brought up during the discussion was the possible recall bias in evaluating the symptoms. A paper on the quality of life from Israel claimed that males with Behçet's disease were doing better than females. The quality of health, relations with close friends and an independent life style were declining whereas attendance to public organizations and the drive for learning were improving (28).

Genetics and pathogenesis

The section on genetics was rather stimulating. There was a search for genetic factors other than HLA-B51 and a whole genome screening of multicas families with Behçet's disease by Karasneh *et al.* revealed linkage on chromosomes 16 and 12 (29). More families and fine mapping of these areas are required for a detailed analysis. Various polymorphisms of the genes of effector molecules with possible roles in disease pathogenesis were studied. The -403 AA haplotype of the chemokine RANTES was more prevalent among the males with Behçet's disease whereas the -2516 AA and -2076 AA haplotypes of the MCP-1 chemokine was more frequent in

females (30). The TNF-1031 allele was significantly associated with the disease independent of gender (31) and ICAM1 469*E variant was more frequently seen in Korean patients (32). The question of methylation of the genes that could have accounted for the gender differences was brought up. The TTbb phenotype for the endothelial nitric oxide synthase gene inferred an odds ratio of 2.42 for acquiring Behçet's disease compared to controls (33) while there were no significant relationships with any polymorphisms related to ID4 and DEK (34), IL-8 receptor CXCR-2 (35), IL-8 (36) and NOD2 gene 3020C insertion mutation (37). A Korean study claimed that there was a relationship between MIC-A*009 and MIC-A*A6 among patients with Behçet's disease (38) and a Tunisian study found that HLA-B51 was more closely associated with the disease compared to the A6 MICA-TM allele (39).

An interesting study on pediatric Behçet patients, revealed an autosomal recessive inheritance pattern contrary to the common belief that the transmission of the disease did not follow a Mendelian pattern (40). A study from Iraq evaluated the acetylator status of the patients and showed that Behçet's disease was seen more often in slow or non acetylators; a factor that was closely linked to the presence of HLA-B 51 (41). A paper claimed that MEVF mutations that characterize FMF were also seen in a group of female patients with Behçet's disease who predominantly had vascular involvement and suggested the possible role of these genes in the disease pathogenesis (42).

There was a consensus among the immunological studies that the inflammatory reaction in Behçet's disease has mainly a Th1 cytokine profile. A study on the skin pathergy reaction from Turkey (43), a Greek study on the immune phenotyping and cytokine profile on peripheral blood lymphocytes (44) and Tunisian and British studies on the *in situ* cytokine expression within the mucocutaneous lesions (45, 46) confirmed this assertion. The only finding that contradicted this was an evaluation of cerebrospinal fluid samples from Turkey which did not fit into any pre-

dominant cytokine pattern (47). A study that attempted to relate HLA-B51 positivity to NK cell activity by determining specific KIR receptors, did not find any special functional role of HLA-B51 with respect to NK cells (48). Histological evaluation of skin lesions of erythema nodosum (49) and papulopustular lesions (50) revealed more episodes of vasculitis compared to controls and the vasculitis was mostly of the leukocytoclastic type with immune deposits in the vessel walls. A study from Greece found increased levels of soluble TNF-receptor-II (p75) serum levels in active patients compared to inactive patients (51) and two studies reported an increase in the sFas-L and BCL-2 levels with inconclusive results on apoptosis (52, 53). Anti *Saccharomyces Cerevisiae* antibodies (ASCA) which are useful in the differential diagnosis of inflammatory bowel diseases, were elevated in a group Israeli patients with Behçet's disease compared to patients with recurrent aphthous stomatitis and normal controls (54) but this was not confirmed in a French study (55). A Russian study found an increased T cell response to retinal S antigen in patients with retinal vasculitis (56) and a study from Netherlands showed a restricted gamma delta T cell receptor usage of undetermined significance (57). There were a number of studies concerning defects in innate immunity and Behçet's disease and a Turkish study that reported decreased levels of mannose binding lectin levels claimed that a defect in innate immunity in the pathogenesis of the disease was possible (58). A decrease in trans-thyretin in the sera of patients with Behçet's disease compared to controls (59) and an increase in the values of L-selectin were also determined (60).

The complexity of the mechanisms underlying thrombosis in Behçet's disease was the main theme in a number of abstracts. An Israeli study found that dyslipidemia was an important factor that differentiated patients with venous thrombosis and controls and showed that total and VLDL cholesterol, triglycerides, apolipoprotein B, C2 and C3 were elevated among these (61). A study from Tunisia revealed that hyper-

homocysteinemia was a risk factor in the thrombosis of Behçet's disease (62) whereas a French study claimed that it was also an independent risk factor for dural sinus thrombosis (63). Impaired relaxation of the brachial arteries and abnormal pulse wave velocity were taken as evidence for endothelial dysfunction (64). The value of procagulant mutations were also evaluated. A study from Turkey showed that deep vein thrombosis was related to Factor V Leiden whereas arterial disease including pulmonary arterial aneurysms was seen more frequently in patients who had the prothrombin gene G20210A mutation and a reduced frequency of PAI-1 promoter 4G/5G insertion/deletion polymorphism (65). There was still no consensus on whether patients with arterial or venous thrombotic disease should be anticoagulated. The previous demonstration of the Factor V Leiden mutation in retinal occlusive disease among a population of Middle Easterners was not confirmed in a UK population suggesting that ethnic differences could be operative (66).

The possible role of infections in the pathogenesis of the disease was also discussed. A study from Japan detected the presence of the streptococcal Bes-1 and Herpes Simplex virus DNA in tissue samples of Behçet patients, but the numbers were too small for a meaningful evaluation (67). The immunogenic proteins of *Streptococcus sanguis* were isolated and it was seen that a 50kDa antigen and elongation factor Tu seemed to elicit a specific response in patients with Behçet's disease (68). A Japanese study evaluated the role of a synthetic human CAP18 peptide (peptides that naturally have anti-microbial and lipopolysaccharide binding properties) and it was determined that the synthetic peptides agglutinated erythrocytes sensitized with purified cell wall or glycolipids from a strain of *Streptococcus sanguis* (69). The potential therapeutic benefit of these peptides remains to be evaluated. Two studies evaluated the cytokine profiles of peripheral mononuclear cells incubated with *Streptococcus sanguis* and both showed that there was a prominent Th1 response with occasional Th2 cytokines

(IL-10), a factor that was taken for evidence of a complex immunological response to streptococci (70, 71). The impaired periodontal health in patients with Behçet's was also related to the possible role of microorganisms in the pathogenesis of the disease (72).

Management

The abstracts on therapy were dominated by interferon and the TNF- blockers. Interferon seemed to be beneficial in suppressing ocular inflammation with a sustained effect after the drug was stopped (73). It also had an acceptable safety profile. The most important drawbacks of the interferon studies were their uncontrolled nature, the lack of standardization of the dosing regimens and the non standardized visual acuity determinations that can easily be influenced by the phase of ocular inflammation (74). A randomized clinical trial of interferon against cyclosporine and/or azathioprine was proposed.

The results of oral tolerization with HSP 60 (p336-351) peptide linked to the cholera toxin B subunit was presented in a small number of patients in an open study (75). It was optimistically claimed that remissions were induced in a subgroup of patients with eye disease (76). A controlled study on the TNF- blocker etanercept revealed that the drug was beneficial in suppressing oral aphthae, nodular lesions, arthritis and papulopustular lesions in the short term while it did not have an effect on the pathergy phenomenon and the monosodium urate tests (77). A six-month open study of etanercept in severe eye disease resistant to azathioprine and cyclosporine, showed that the drug was beneficial in at least maintaining visual acuity although the effect was not sustained when the drug was stopped (78). There were various case reports and uncontrolled studies on the beneficial effects of infliximab, another anti-TNF agent, especially on uveitis (79-83). Another uncontrolled study claimed that pentoxifylline was beneficial in controlling the severity of oral and genital ulcers (84) and a study from Iran proposed that methotrexate was effective in eye disease (85).

A survey among the conference atten-

dants disclosed that there were still many divergent opinions among the physicians on how to manage their patients. The magnitude of these differences was quite similar to that observed during the 8th International Conference 4 years ago during which the same questions were asked. There was however one, perhaps important difference. According to the current survey significantly more physicians were using azathioprine for prophylactic purposes in the high risk, young male patient.

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