Workshop Report

Ninth International Conference on Behçet's Disease, Seoul, Korea, May 27–29, 2000

Hippocrates was likely the first to recognize the characteristic symptoms of what we know today as Behçet's disease (BD). This disease is named after Hulusi Behçet, who described the symptom complex of recurrent oral aphthous ulcer, genital ulcer, and uveitis as a disease entity in 1937. As more and more patients were diagnosed with BD in the following years, an international study group was founded to explore the pathogenesis of this disease and to exchange research results and opinions on BD. According to S. Lee, the term "Behçet's disease" is used more often than "Behçet's syndrome" in current literature.

Since 1964, international conferences on Behçet's disease were held in Rome, Istanbul, Tokyo, London, Rochester, Paris, Tunis, and last in Reggio Emilia in 1998. At the recent conference in Seoul, Korea, clinicians and scientists from more than 20 different countries met again to continue this discussion and exchange on BD. On this occasion the International Society for Behçet's Disease was inaugurated, "to extend and communicate knowledge about BD." It is anticipated that the study, research activities, education and communication, awareness, and management of BD will continue to expand.

EPIDEMIOLOGY

BD is a universal disorder, with varying prevalence in countries near the so-called silk route as well as in non-silk route countries (Zouboulis). In Turkey, the prevalence rate has been found to be 80–370 patients per 100,000 inhabitants. The results of a new preliminary study from Istanbul revealed a prevalence of 320/100,000 (Azizlerli). The prevalence of the disease is 2–30 patients/100,000 in the Asian continent and 0.1–7.5/100,000 in Europe and the USA. New data from Korea and Iraq suggest a prevalence of 18/100,000 (Roh) and 17/100,000 (Sharquie), respectively. The prevalence rates appear to depend not only on the patients' ethnic origin but also on the geographic area they are currently living in. In a cohort of US patients, more female patients were found than in silk-route cohorts (Calamia). Male patients were overrepresented in this group with large vessel disease. Familial occurrence has been reported in 1–18% of the patients, primarily in the Turkish, Israeli, and the Korean population. Taken together, these data are consistent with environmental triggering of a genetically determined disorder.

DIAGNOSIS AND PROGNOSIS

Diagnostic criteria for BD have been established by different centers, and by the International Study Group (ISG). However, especially in the incomplete form, diagnosis of BD may still be delayed as much as 2–15 years after onset of disease. M.A. Chamberlain stressed that such delay is of significance, as early treatment, especially to prevent blindness, is more effective. N. Dilsen discussed his own set of criteria including oral and genital ulcerations, eye lesions, thrombophlebitis, and positive skin pathergy test. Any 3 of these occurring during the disease would be enough for a definite diagnosis of BD. Others confirmed the performance of the ISG criteria in correctly classifying BD (Tunç). In the US and for retrospective studies in which patients were not systematically tested for pathergy, the classification tree may be the most sensitive criteria (Calamia).

Oral aphthous ulcers represent the initial manifestation of the disease in the majority of patients worldwide (47–86%), whereas at onset of BD genital ulcers are present in only 2–10% of the patients (Zouboulis). Genital ulcers may occur together with or after the development of oral ulcers and usually persist over 10–30 days. After larger genital ulcers, scarring is frequent and is an important finding to support a suspicion of BD (Göksügür).

A number of studies confirmed that male sex, early age of onset of disease in adults, and HLA-B51 positivity are markers for severe prognosis in BD. Additional factors related to prognosis are a delay in diagnosis and lack of treatment (Dilsen, Benamour). Mortality rates for the disease are between 0 and 6%. In Iran, a country with a high prevalence of BD, patients have had milder forms of BD since 1993 (Shahram). Possible reasons include the earlier diagnosis of the disease or a change in clinical pattern of the disease. No such changes were reported for Iraqi patients (Sharquie). Although rare, amyloidosis in BD carries a 50% mortality over 3–4 years (Melikoglu). Cancers were found to be rare in patients with BD in Iran (Shahram). Four of 10 tumors in 4130 cases were seen in patients treated with oral cyclophosphamide; no cancers were detected after pulse cyclophosphamide.

Efforts continue to develop tools for the assessment of disease activity in BD, and these remain a priority for the near future (Chamberlain).

CLINICAL MANIFESTATIONS

Oral aphthous ulcers (92–100%), genital ulcerations (57–93%), skin lesions (38–99%), ocular lesions (29–100%), and arthropathy (16–84%) are the most frequent clinical features of BD. The presence of oral, ocular, and/or genital lesions, however, can also occur in patients with erythema multiforme, mucous membrane pemphigoid, and the vulvovaginal-gingival form of erosive lichen planus. As all 3 conditions may be confused with BD, R.S. Rogers III referred to them as pseudo-Behçet's disease. The variable clinical features of the skin lesions were emphasized in several reports. Typical acne was no more frequent in BD than in controls, and should be distinguished from the pustulosis (pseudofolliculitis) of BD (Chams-Davatchi). However, androgen receptors were higher in papulopustular lesions in BD than controls, suggesting that these may play a role in these lesions (Durusoy). Cutaneous ultrasound was highly specific in distinguishing erythema nodosum lesions from superficial thrombophlebitis (Kucukoglu). Perigenital and anal aphthous lesions may occur, especially in children (Zouboulis) and epididymitis, orchitis, prostatitis, and ovarian cysts are seen in a few patients. The positivity of the pathergy test varies widely (6–71%), but according to N. Dilsen it should still be applied to every patient more than once, with 2 thick needle pricks (20–22 gauge), read at 48 hours. I. Fresko reported a greater sensitivity (78% compared to 28% for pathergy) and a better reproducibility by measurement of the cutaneous response to the intradermal injection of monosodium urate crystals than with the pathergy test. A concordant response was observed in 95% of the patients after one year. An oral pathergy test was found to have similar sensitivity to the skin test in Iraqi patients with BD (Shaquie). Local irritating factors were found to play a role in oral aphthosis, especially of the anterior tongue and buccal mucosa (Ahn).

Blindness is frequent in BD in Morocco (S. Benamour), the main cause being lack of early and correct management. F. Davatchi reported that the outcome of the eyes was not correlated to the duration of the lesions, as long as treatment was pursued during active disease and cytotoxic drugs were changed in case of ineffectiveness.

According to C.G. Barnes, the prevalence of arthritis has been shown to be 45–50%, with an even higher incidence of arthralgia. The arthritis may be oligoarticular or polyarticular, intermittent or chronic, with knee involvement most typical. It does not regularly include sacroiliitis or spondylitis and should not be classified with the seronegative spondyloarthropathies, yet the incidence of ankylosing spondylitis was found to be higher than in the control population (not given) in Iran (Nadji). Unusual manifestations include a deforming or erosive arthropathy. Acute monoarthritis, myalgia, myositis, bone infarction, and avascular osteonecrosis were much less common (Benamour). Two studies pointed to the association of arthritis and skin lesions (Tunç, Kaklamani).

The French experience with dural sinus thrombosis in 36 patients was presented (Wechsler). Treatment consisted of anticoagulants, corticosteroids, and colchicine in the majority, with immunosuppressives reserved for those patients with uveitis or central nervous system involvement. The prognosis of treated patients was generally good. Central nervous system involvement was the presenting manifestation of BD in 5 patients out of 15 with the complication in Shiraz in southwestern Iran (Khosravi). Magnetic resonance image (MRI) scanning was confirmed as a sensitive test in neuro-Behçet. Subclinical MRI lesions were found in some BD patients that did not evolve to clinical disease (Grana), as previously reported in some Japanese patients (Ohya). The potential value of SPECT analysis for the evaluation of cerebral blood flow alterations was discussed (L. Emmi).

The frequency of ileal and colon abnormalities in BD was found to be 41% in Koreans studied by colonoscopy (Kang). In another study from a different center, all 22 patients who had previously undergone intestinal resection had ulcerations at the anastamotic site when visualized by colonoscopy (Kim). The need for re-operation in BD patients who required operation was common (Kim). Compared to patients with Crohn's disease the ulcers of BD were more likely to be deeper and discrete, round or oval rather than linear, and were focal in distribution rather than segmental or diffuse (Lee).

Vascular manifestations are a major cause of morbidity and mortality in BD. These complications, often multiple, were reported in 33% of patients from Saudi Arabia (Al-Dalaan) and in 14% of patients from Shiraz (Samangooei).

IMMUNOGENETICS AND PATHOGENESIS

BD is a systemic inflammatory disease, the cause of which is still unknown. It is believed that BD is triggered by exogenous environmental factors in individuals with a background genetic susceptibility. S. Ohno reviewed studies that show that BD is closely associated with HLA-B51, especially HLA-B*5101, in a number of populations. Although in lower frequency, HLA-B*5108 was also found in German (8%) and Turkish (19%) patients with BD, and an increased incidence of HLA-B*51x homozygosity is observed in both populations (Kotter). Linkage of HLA-B locus with BD was reported, for the first time, in Turkish patients, and the contribution of HLA-B to the overall genetic susceptibility to BD was estimated to be 12–20% (Gul). There was no association of HLA-B51 heterozygosity and homozygosity with any specific manifestation or a more severe course (Gul). The association of MHC class I chain related gene A (MICA), first suggested by Ohno, was described in Korean patients with MICA6, present in 50% of BD patients compared to 26.5% of controls (relative risk 2.8), with a

higher risk also in homozygotes (relative risk 6.1) (Cho). In other studies for genetic markers, no associations of BD with tumor necrosis factor alpha (TNF-α) or interleukin 6 (IL-6) gene promoter regions were observed (Duymaz, Gul); however, a weak association with intercellular adhesion molecule-1 E469 gene polymorphism was found (relative risk 2.1) (Madanat). Another association with TAP2 (transporter associated with antigen processing 2) genes, which have an essential role in the antigen presenting system, was also reported from Korea with TAP2*A/*A, TAP2*C/*C, and TAP2*A/*C frequencies increased (Mok). Finally, some familial Mediterranean fever related pyrin mutations (E148Q and P706) were found with higher frequency in patients with BD, suggesting that pyrin mutations may act as additional susceptibility factors in BD (Touitou).

On this genetic background, T. Lehner summarized some of the possible immunopathogenetic mechanisms in BD. Microbial or other stress factors might stimulate heat shock proteins (HSP) and MICA gene products, resulting in significant upregulation of γδ+ T cells. These T cells might then generate a number of ß-chemokines, functioning as innate adjuvants, enhancing cellular and humoral immune responses by the mucosal as well as the systemic route. Together with IL-12, ß-chemokines induce Th1 polarization in BD. Stimulation of peripheral lymphocytes with human HSP60 immunodominant peptides increased CD3+, αß+ T cell receptor positive T cells, whereas bacterial extracts (*Streptococcus sanguis* and *Escherichia coli*) caused a more cytotoxic pattern, suggesting that innate immunity is possibly also activated (Direskeneli). In an experimental mouse model, heat shock to oral mucosal surface increased the colonization of *S. sanguis*. Inflammatory cytokines were detected in the mucosa and a mild neutrophil infiltration of the eye was observed. Granulocyte colony-stimulating factor transgenic mice also had more severe disease after *S. sanguis* inoculation (Isogai). As G-CSF is a priming agent of neutrophils, hypersecretion of proinflammatory cytokines due to possible genetic defects could be another contributor to unregulated inflammation in BD. In another animal model, herpes simplex virus inoculation of ICR mice did not develop BD when macrophages were knocked out, and induction of Th2 cytokine production attenuated BD symptoms, suggesting that Th1 cytokines drive the inflammation (Sohn). Th1 cytokines interferon-γ and IL-12 were also increased in patients' sera, but the antiinflammatory cytokines IL-10 and transforming growth factor-ß1 were also elevated (Ben Ahmet, Assaad-Khalil).

Elevated IL-8 levels were found in BD patients with active disease and in human endothelial cells in culture with Behçet's sera. IL-8 production by these cells was inhibited by agents used in the treatment of the disease, especially interferon-α-2a and cyclosporin A (Zouboulis). IL-8 was suggested as a reliable marker for disease activity (Katsantonis). In a search for other laboratory markers of disease, $ß_2$-microglobulin and serum amyloid A were suggested to have higher sensitivity in active disease (70–80%) compared to erythrocyte sedimentation rate and C-reactive protein (20–35%) (Aygunduz). Serum levels of another α-chemokine, GRO-α, and ß-chemokines MCP-1 and RANTES were also elevated (Bozkurt).

D.O. Haskard showed that administration of vitamin C increased flow mediated dilatation in BD, rapidly reversing vascular endothelial dysfunction. These results suggest that vascular endothelial dysfunction might be due to oxidant stress. Direct activation of endothelial cells was observed with IgM antiendothelial cell antibodies through intracellular protein kinases and induced expression of surface intercellular adhesion molecule-1 (Cho).

MANAGEMENT AND NEW THERAPEUTIC APPROACHES

S. Assaad-Khalil recognized that the ideal therapy of ocular manifestations is not at hand, and combination therapy may be more beneficial. The therapeutic choice must be individualized and guided by accurate ophthalmologic assessment. Several therapeutic approaches for ocular disease were presented. (1) F. Davatchi reported an improvement of visual acuity with pulse cyclophosphamide and prednisolone compared to prednisolone alone in a double blind crossover study, whereas inflammatory indexes improved in both groups. (2) Combination therapy with low dose pulse cyclophosphamide and methotrexate was superior to single therapy with the same drugs (Shahram). (3) Experiences were expanded regarding treatment with interferon-α (Kotter), in combination with azathioprine (Hamuryudan), with high dose corticosteroids at induction (Adler), and in disease resistant to immunosuppressive agents (Wechsler). Longterm remissions were seen in ocular disease (Koetter) and in the treatment of mucocutaneous disease (Boyvat). Interferon-α may affect cytokine networks, especially through soluble TNF receptor p75 (Direskeneli), and may inhibit retinal angiogenesis (Stuebiger). The chance of improving vision after vitrectomy appears limited (Karkhaneh).

Thalidomide was found to be useful in one patient with recurrent episodes of intestinal disease (Hamuryudan). Thalidomide tends to decrease TNF-α receptor levels and CD8/CD11ß+ T cells and natural killer cells in early treatment, and increases CD4+CD45RO+ memory T and γδ+ T cells later in BD (Direskeneli). Mycophenolate mofetil was not helpful in a small number of patients with mucocutaneous disease (Zouboulis). Dapsone was reported to be helpful in several disease manifestations (Sharquie).

Aggressive medical management should be given when surgery for aneurysm or valve replacement is required (Kwak, Zhuoli, Lee) to reduce mortality and recurrences. Finally, as a less toxic, immunomodulatory approach, toler-

ization with a human heat shock peptide responsible for uveitis in rats was suggested as a possible strategy for future treatment of BD by T. Lehner.

The conference provided a good opportunity for all participants from silk route and non-silk route countries to discuss recent data and results against a background of current theories of the etiopathogenesis of BD. It is anticipated that the International Society for Behçet's Disease will further promote interest and studies in the disease. The Tenth International Congress on BD is planned for Berlin, Germany, in 2002.

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