Meeting Report

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Behçet's disease (BD) is a multisystemic, chronic, relapsing inflammatory disorder classified among the vasculitides, the cause of which is still unknown. Since 1964, international meetings on BD were held in Rome, Istanbul, Tokyo, London, Rochester, Paris, Tunis, Reggio Emilia, Seoul, Berlin, Antalya, and last in Lisbon in 2006. At the recent conference in Pörtschach, Austria, 170 clinicians and scientists from 22 countries met to continue the multidisciplinary exchange on this disease. More than 130 abstracts were presented, providing the most recent data on epidemiology, diagnostic methods, clinical manifestations, pathogenesis, and therapeutic options in BD. A selection of these reports is summarized here.

EPIDEMIOLOGY

BD is a universal disorder, with varying prevalences in countries near the so-called Silk Road as well as in non-Silk Road countries. N. Dilsen reviewed the current data on prevalence rates in the USA (0.33 per 100,000), Germany (0.55–20.75 per 100,000), England (0.64 per 100,000), Sweden (1.18 per 100,000), Portugal (1.53 per 100,000), Italy (2.5 per 100,000), Japan (13.5 per 100,000), Saudi Arabia (20.0 per 100,000), Iran (100.0 per 100,000), and Turkey (80–370.0 per 100,000). New data from Olmsted County, Minnesota, USA, suggest a higher prevalence of BD (5.2 per 100,000) in this region, comparable to that in Southern Europe (K.T. Calamia). In BD cohorts from silk-route countries men are predominately affected, whereas women are overrepresented in groups from European countries and the USA (K.E. Sharquie, M. Smiti-Khanfi, report of the International Team for the Revision of the International Criteria for Behçet's Disease; 2006).

DIAGNOSIS AND ASSESSMENTS

Criteria for the diagnosis and classification of BD have been published by different centers, the criteria of the International Study Group (ISG) being the most widely accepted. Although these criteria were primarily intended to be used for the classification of patients with BD in clinical studies, these criteria have also been used for diagnostic purposes (F. Davatchi). However, due to the relatively low sensitivity of the ISG criteria, the diagnosis of BD is still delayed in numerous cases (A. Gul, F. Davatchi). In 2006, the International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) developed a new set of diagnostic criteria based on the clinical findings of 2556 patients with BD and 1163 controls from 27 countries. Since then the performance of these International Criteria for Behçet's Disease (ICBD) have been evaluated in 4 countries (Germany, Iran, China, Spain) in 6521 patients and 3564 controls (A. Altenburg, F. Davatchi, Z. Zhang, J. Graña). Overall, the ICBD had a sensitivity of 87.0%–98.2% and a specificity of 73.7%–95.6%. In comparison with 14 other diagnostic or classification criteria for BD (including the ISG criteria), the ICBD had a relatively high sensitivity and a moderate specificity.

C. Zouboulis emphasized the importance of a correct classification of oral ulcers in the diagnostic approach to BD. In a set of 984 patients with oral ulcers and suspected BD, only one-third of patients had lesions compatible with BD aphthae (C. Chams-Davatchi). M. Daneshpazhooh found that aphthous lesions were mistakenly thought to be present in 89% of cases in a series of consecutive patients with pemphigus vulgaris.

Positive skin pathergy reaction was reported with a high frequency (44%–77%) in most silk-road countries, whereas positive test results were less common in Europe and the USA (F. Davatchi). Immunosuppressants such as colchicine, azathioprine, cyclosporine, and interferon-α 2b did not affect the results of the pathergy test in a Turkish cohort (K. Tascilar). In Iran, the incidence of pathergy phenomenon has been gradually decreasing during the past 30 years (> 60% positive test results before 1977 compared to < 45% positive tests after 1998) with no plausible explanation (F. Davatchi).

Nailfold capillaroscopy showed anomalous findings of the microcirculation in 40% of 128 patients with BD in an Iranian study. Enlarged capillaries (26%) and hemorrhages (16%) were the most common abnormalities described, and they were associated with an increased risk of high blood pressure (OR 4.2) and phlebitis (OR 5.5) (A. Movasat). Progression of macrovascular damage in patients with BD was reported in a longitudinal ultrasound study showing a

mean 20% increase of intima-media thickness (carotid artery) and a 35% increase of augmentation index (brachial artery) in BD patients after 6 years (A. Protogerou).

For the assessment of BD disease activity in clinical routine, a new patient questionnaire, the Behçet's syndrome activity score (BSAS), was proposed. BSAS revealed a moderate correlation ($corr_{coeff}$ = 0.65) with the established Behçet's disease current activity form (C. Forbess). G. Mumcu presented a composite score for the assessment of oral ulcers including the number and duration of ulcers, patient's pain, and functional disability as well as the global assessment of ulcer activity by the clinician and the patient. The Turkish version of the EuroQol-5D was found to be useful for BD patients with mucocutaneous and joint disease but not for patients with serious organ involvement (N. Sut).

IMMUNOGENETICS AND PATHOPHYSIOLOGY

It is widely believed that BD is triggered by exogenous, environmental factors in individuals with a background genetic susceptibility, for example, by HLA-B51. A. Mahr performed a metaanalysis on the predictive value of HLA-B51 determination using data from 2,896 BD patients and 11,078 controls. Overall, the OR for the presence of BD was 6.04 (95% CI 4.96–7.35) in HLA-B51-positive individuals. However, regional differences were observed, with a higher OR in the Middle East (6.93) and Southern Europe (7.65) compared to Northern Europe (4.91). In Iran, HLA-B51-positive patients more often had erythema nodosum, joint involvement, myocardial infarction, arterial thrombosis, and a positive pathergy test than HLA-B51-negative individuals (F. Davatchi). In a German study, HLA-B51 was associated with erythema nodosum-type lesions and ocular involvement (A. Altenburg). The combination of HLA-B51 and HLA-A2 (HLA-A2/B51) loci was linked with genital lesions in Japanese patients with BD (T. Kobashigawa).

Other studies on HLA class I molecules showed a high prevalence of HLA-A2 (66.5%) in German and Turkish BD patients (A. Altenburg), as well as an increased risk of BD in Iranian HLA-B27-positive individuals (OR 3.69) (A. Nadji). HLA-B27-positive patients frequently showed an overlap of BD with ankylosing spondylitis (OR 14.6), and often presented with gastrointestinal manifestations (OR 2.3–3.5) and glomerulonephritis (OR 21.3). HLA-A26 was related to eye involvement in Japan (T. Kobashigawa) and HLA-Bw4 was associated with arthropathy and lung, eye, and central nervous system (CNS) manifestations as well as a positive pathergy reaction in Germany (A. Altenburg).

CTLA4 polymorphisms were reported to be linked with an increased CTLA4-1661 G/G genotype (OR 5.2) and CTLA4 –1722T –1661G –318C promoter haplotype (OR 2.6) (K.S. Park); or a decreased CTLA4 –1722T –1661A –318T promoter haplotype (OR 0.1) and CTLA4 +49G allele (OR 0.2) (I.B. Dhifallah); or no risk of BD in studies from Korea, Tunisia, and the UK, respectively (G.R. Wallace).

Higher frequencies of the interferon receptor 1 and interferon receptor 2 genotype combinations –18417GG/–11876GG (OR 2.696) and –18417CC/–11876GT (OR 7.835), respectively (S. Pay), the killer immunoglobulin-like receptors (KIR) gene variant KIR3DL1*001 in HLA-Bw4-positive cases (OR 1.5) (J. Duymaz-Tozkir), and the interleukin 18 promoter –607 CC genotype (OR 2.3) were observed in BD patients compared to healthy controls (F. Keskin). A VNTR polymorphism in the P selectin glycoprotein ligand 1 (PSGL1) with higher frequencies of the B allele (OR 2.0) and the AB genotype (OR 2.25) were found to be associated with the occurrence of thrombotic events in Turkish patients with BD (F. Cosan).

Involvement of microbial pathogens has been suspected in the pathogenesis of BD. G. Mumcu showed increased salivary concentrations of the antimicrobial peptides HNP 1-3 in BD patients compared to healthy controls, and these HNP 1-3 levels correlated with the occurrence of severe BD organ manifestations. In Korea, BD patients were more likely to have a positive history of tonsillitis and dental caries than controls, and BD patients with persistently elevated levels of anti-streptolysin O (ASL-O) more frequently had erythema nodosum than patients with normal ASL-O titers (S. Ho Oh).

Microbial pathogens may stimulate the innate immune system of BD patients through Toll-like receptors (TLR). J.E. Do demonstrated an increased surface expression of TLR2 and TLR4 on monocytes of patients with active BD compared to healthy controls. Serum levels of vitamin D_3 were inversely correlated with TLR2 and TLR4 expression, and *in vitro* data revealed a dose-dependent suppression of protein and mRNA expressions of TLR2, TLR4, and tumor necrosis factor-α (TNF-α) synthesis in monocytes by vitamin D_3. M. Takeno described increased TLR-4 expression and reduced heme oxygenase 1 (HO-1) mRNA levels in peripheral blood cells from patients with active BD compared to controls. HO-1 is an inducible heme-degrading enzyme with antiinflammatory properties, and stimulation of TLR4 is known to suppress the production of HO-1. In contrast to these studies, D. Vassilopoulos found no difference in the expression of TLR1, TLR2, TLR3, TLR4, and TLR9 of peripheral T cells and monocytes in Greek patients with BD compared to controls.

NKG2D, another innate immune receptor, was less frequently expressed on circulating natural killer (NK) and CD8-positive and γδ-positive T cells in BD compared to controls. Whether this lack affects the cytotoxic capacity or other functions of NK and CD8-positive and γδ-positive T cell populations has not been investigated (S. Seema).

Several lines of evidence point to a polarized T-helper-1 (Th1) immune response in BD. Studies presented at this meeting, however, suggested a role of Th2 reactions as well.

J.S. Lee reported that T cell immunoglobulin mucin-3 (TIM-3), a molecule involved in Th1-mediated immune responses, was downregulated in peripheral blood cells of patients with active BD compared to controls. S. Pay observed increased numbers of interferon-α (IFN-α)-producing plasmacytoid dentritic cells (pDC) and increased levels of IFN-α paralleled by the absence of IFN-ß in cell cultures from patients with BD. Elevated levels of IFN-α are usually found in diseases characterized by a Th2-type immune response such as systemic lupus erythematodes.

Vascular injury likely plays a central role in the pathogenesis of BD. Increased plasma levels of endothelial cell-activated protein C receptor (EPCR) have been observed in BD patients and were considered to reflect the occurrence of vascular damage (F.N. Yalçındag). R. Marcolongo observed reduced prevalences of circulating endothelial progenitor cells in BD patients compared to controls, indicating potential impairments of endothelial repair.

Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) have been implicated in the pathogenesis of BD-related ulcers. Salivary levels of VEGF were 2-fold higher in BD patients with active oral aphthae compared to patients with no ulcers and controls. Expression of EGFR was reduced in buccal swabs from BD patients with oral aphthae compared to patients without ulcers. However, EGFR expression did not differ between BD patients and controls (E. Hagi-Pavli).

CLINICAL MANIFESTATIONS AND COURSE

BD is a multisystemic chronic disorder with different clinical features and a variable prognosis. Disease course can be mild during the first years, but major organ involvement has still been reported 3 years after disease onset in 43% of cases in a Turkish cohort (V. Hamuryudan). Risk factors for a poor outcome of BD were non-aphthous onset, positive family history, male gender, younger age at disease onset (< 25 years), and long disease duration (N. Dilsen).

Prevalences of oral and genital aphthae were found to be 98.1% and 76.9% in the ITR-ICBD cohort, respectively. Lower frequencies of oral aphthae were reported in Greek compared to Italian BD patients (G. Vaiopoulos) and a higher ulcer recurrence rate was present in British (3.3 ± 2.8 ulcers per month) compared to Turkish (1.5 ± 2.5 ulcers per month; G. Mumcu) and Israeli patients (10.2 ± 12.3 ulcers per year; I. Krause). Genetic diversity and environmental factors such as differences in oral healthcare were considered to contribute to these divergent observations (G. Mumcu).

Gastrointestinal (GI) tract involvement in BD may be associated with abdominal pain and bloody diarrhea. J. Crespo emphazised that the differentiation of BD with GI symptoms and inflammatory bowel disease (IBD) mimicking BD may be challenging, as patients with IBD also present with recurrent oral and genital aphthae, skin lesions, and ocular inflammation. In a Portuguese cohort of patients with Crohn's disease and ulcerative colitis the ISG criteria for BD were formally fulfilled in 6.3% and 3.8% of patients, respectively.

The frequency of skin lesions was found to be 60.1% in Greeks (compared to 71.9% in the ITR-ICBD cohort). Erythema nodosum was more common in women, was localized mainly in the legs, lasted for a few weeks, and recurred rarely. In contrast, pseudofolliculitis was more prevalent in men, was widespread over the body, and showed variable duration with frequent recurrences (G. Vaiopoulos).

Ocular manifestations were present in 53.7% of patients in the ITR-ICBD cohort. Panuveitis was the most common form of uveitis in Korea (58.4%), whereas anterior uveitis (28.9%) and posterior uveitis (12.7%) were less frequent (H.G. Yu). According to H. Chams the most frequent causes of blindness in BD are chorioretinal vasculitis and its consequences including optic atrophy, macular scar, chorioretinal atrophy, and vascular necrosis. Risk factors for blindness were long duration of uveitis and retinal vasculitis, low visual acuity at the first visit (Iran, Korea), and posterior segment involvement (Korea) (H. Chams, H.G. Yu).

Joint involvement occurs in up to 50% of patients with BD in Morrocco (50.5% in the ITR-ICBD cohort; W. Bono). Arthritis in BD is usually nondestructive, nonsymmetric, and affects predominately the knees (24.7%–56.6%), wrists (44.9%–53.9%), and shoulders (18.0%–46.1%) (I. Krause). Sacroiliitis (radiological grade I-II) has been observed in 10.5%–22.4% of BD patients (A. Elonakov). Most patients have oligoarticular or polyarticular involvement, whereas monoarthritis is rare, as shown by a Tc-99m-HDP bone scintigraphy study (E.C. Han). A particular cluster of disease expression in BD is the combination of acne and arthritis that may also include enthesopathy but not sacroiliitis or HLA-B27 (G. Hatemi).

The frequency of large-vessel involvement in BD was 15% in a cohort of 5970 BD patients in Turkey, which is comparable to the prevalence observed in the ITR-ICBD cohort (18.2%). In the Turkish study, more than 90% of affected cases were men; 76% of vascular events occurred either at disease onset or within the first 5 years of disease (M. Melikoglu). The most common vascular manifestations were deep-vein thrombosis of lower extremities (78.5%), followed by pulmonary artery aneurysms (5%) and superior vena cava syndrome (5%). Less common vascular complications (< 5%) included peripheral artery aneurysms, cerebral venous sinus thrombosis, inferior vena cava thrombosis, Budd-Chiari syndrome, aortic and carotid artery aneurysms, mesenteric artery aneurysm, and splenic artery thrombosis (M. Melikoglu, S. Hammami). F. Cosan emphasized the importance of screening for pulmonary artery aneurysms, a potentially life-threatening complication of BD. Pulmonary artery aneurysm should be suspected in cases of hemoptysis, dyspnea, and chest pain, if acute-phase proteins are persist-

ently elevated and/or if extrapulmonary vascular manifestations are present. The diagnosis should be proved by computer tomography as chest radiography lacks specificity.

Prevalences of neuro-Behçet vary between 2.2% and 59% depending on the definition of neuro-Behçet, ethnicity of the cohorts, and study settings. According to A. Al-Araji, neuro-Behçet is present if the neurological syndrome is caused by BD, supported by one or more relevant additional investigations (neuroimaging, cerebrospinal fluid, neurophysiology), and if there is no alternative diagnosis. Neuro-Behçet can be classified as acute or chronic, progressive, parenchymal or nonparenchymal, and mixed-type disease. In a Japanese cohort only one out of 56 patients was diagnosed with nonparenchymal neuro-Behçet (dural sinus thrombosis), and 23% of patients had chronic progressive parenchymal neuro-Behçet. These patients were older (36.5 vs 47.4 yrs, respectively), more frequently male (50% vs 85%), and were less responsive to corticosteroids and DMARD compared to patients with acute neuro-Behçet (A. Suda). The most common neurological complaints in Jacksonville, Florida, USA, were motor/sensory stroke-like deficits (65%) and headache (50%) (P.L. Konieczny). Headache in BD patients may be caused by primary headache syndromes (e.g., tension-type headache, migraine — 50% of cases), by the so-called "Behçet-headache" (10%), neuro-Behçet associated with headache (10%), or uveitis (3%). It was recommended the cause of headache be investigated in a patient with known BD in cases of recent onset, severe headache, or a change in character, with an onset together with systemic flare and/or presence of other neurological symptoms (A. Al-Araji).

THERAPY

Corticosteroids and immunosuppressants are used for the treatment of BD. G. Hatemi presented the recently published EULAR recommendations for the management of different manifestations of BD based on a systematic literature review. Recommendations related to the eye, skin-mucosa disease, and arthritis were mainly evidence-based whereas recommendations on vascular disease and neurological and GI involvement were more heavily dependent on expert opinion and uncontrolled evidence from open-label clinical trials and observational studies.

Several therapeutic approaches were presented for ocular disease: (1) Interferon-2α (IFN-2α) treatment resulted in better mean visual acuity and lower rates of recurrences compared to cyclosporin A according to a retrospective analysis from Germany (L. Krause). Fifty percent of BD patients with uveitis of the Tübingen cohort remained in longterm remission after therapy with IFN-α. Side effects were reported in up to 95% of treated patients including headache, fatigue, hair loss, itching, reddening at site of injection, fever, leukopenia, thrombocytopenia, and depression (L. Krause, I. Kötter). (2) F. Davatchi demonstrated the efficacy of a combination therapy with azathioprine, prednisone, and cyclophosphamide (CYC) pulses for treatment of posterior uveitis and/or retinal vasculitis in a nonrandomized trial showing improvement of disease activity and visual acuity. (3) W. Bono presented a successful combination strategy of intravenous methylprednisolone pulses and pulse-CYC for treatment of patients with severe posterior uveitis, panuveitis, and/or retinal vasculitis. (4) Intravitreous triamcinolone, intravenous methylprednisolone, and a single infusion with infliximab were prospectively compared in patients with a sight-threatening relapse of panuveitis (N. Markomichelakis). Although all 3 treatment modalities were comparably effective after 4 weeks, infliximab showed the fastest response and intravitreous triamcinolone had the highest number of adverse events (57.1% ocular hypertension, 28.6% vitrectomy). Y. Horie observed a similar high rate of complications with intravitreous triamcinolone, including ocular hypertension and cataract progression in 57% of cases each. (5) Rituximab was used in a pilot study by F. Davatchi to treat 10 patients with therapy-resistant retinal vasculitis. Overall, an improvement of ocular disease activity was seen after 6 months, but visual acuity improved in only half the patients. In another pilot study of rituximab treatment, an improvement of chronic macular edema was observed in more than two-thirds of patients with retinal vasculitis (H. Chams). (6) Infliximab was given to 10 patients with severe therapy-resistant ocular involvement, resulting in a stabilization of mean visual acuity and a reduced number of ocular attacks per month (Y. Ozyazgan).

For BD patients with predominant oral-mucosal disease topical corticosteroids, tacrolimus, and viscous lidocaine or systemic colchicine, dapsone, or thalidomide have been used with varying success. Interferon-α sublingual tablets led to a 50% reduction of the frequency and duration of oral ulcers in a pilot trial by S. Assaad-Khalil. Topical tacrolimus was shown to increase the duration of ulcer-free days, to reduce the average number of ulcers, and to decrease patients' pain scores after 8 weeks of treatement. Side effects occurred transiently in > 85% of patients including burning, tingling, and dryness during drug application (J.Y. Roh).

There are no controlled data on the management of CNS involvement in BD. Agents that have been suggested for treatment of parenchymal neuro-Behçet include corticosteroids, IFN-α, azathioprine, cyclophosphamide, methotrexate, chlorambucil, and TNF-α antagonists. Dural sinus thrombosis should be treated with corticosteroids. No consensus was obtained on whether anticoagulants should be used (A. Al-Araji). Methotrexate and infliximab may be effective to treat chronic progressive neuro-Behçet, whereas corticosteroids, pulse-CYC, and azathioprine lacked efficacy (H. Kikuchi). Cyclosporin A should not be used in patients with CNS disease, because of an association with brain involvement, unless it is necessary to suppress intraocular inflammation (G. Hatemi).

BEHÇET'S DISEASE IN CHILDREN

Pediatric BD occurs before the age of 16 years (peak 11 years) and is defined by the same diagnostic/classification criteria as in adults (G. Akman-Demir, F.Z. Alaoui). F. Shahram compared the diagnostic value of the ICBD and ISG criteria in a cohort of 265 pediatric BD and 250 control patients from Iran. They showed a sensitivity of 98.1% and 72.5% as well as a specificity of 97.6% and 100%, respectively.

Data on epidemiology are scarce, but in Italy and France the prevalence of pediatric BD was reported to be 1 per 150,000 children (I. Koné-Paut). In comparison with BD cases of all ages, the proportion of pediatric BD is low (2.4%–6.9%) (G. Akman-Demir, F. Shahram).

The most frequent clinical manifestations of pediatric BD patients were oral (97%) and genital aphthosis (57%), skin lesions (36%), and joint involvement (16%) in a cohort from Iran (N. Shafaie). The prevalence of eye involvement varied from 9.3% to 90% in different populations (I. Koné-Paut). It appears that ocular disease in pediatric BD is associated with a better prognosis than in adults, as > 90% of children maintained visual acuity of > 0.1 despite recurrent flares in a Japanese study (S. Ohno). Nevertheless, complete loss of vision may occur in a few patients (I. Koné-Paut). Neurological involvement has been observed in 2.5% and 16.3% of cases in Morrocco and Turkey, respectively (F.Z. Alaoui, G. Akman-Demir). In the patients' group from Morocco only parenchymal CNS manifestations and cranial nerve palsies were described, whereas in the Turkish cohort 84% of cases had dural venous sinus thrombosis.

Current strategies to treat pediatric BD are similar to therapeutic concepts in adults, although most drugs are not approved for use in children (I. Koné-Paut). Colchicine, nonsteroidal antiinflammatory drugs, glucocorticoids, and immunosuppressants may be used for mucocutaneous and joint manifestations. For patients with severe aphthosis, thalidomide is a possible therapeutic option. In cases of severe ocular disease, IFN-2α or anti-TNF-α inhibitors can be considered. TNF-α-blocking therapy may also be useful for neurological and GI disease manifestations.

SUMMARY

BD patients should be managed with an interdisciplinary approach to guarantee optimal care of clinical manifestations. This conference in Pörtschach was held under the presidentship of Prof. H. Yazici, Istanbul, Turkey, and provided a good opportunity for all participants to discuss recent data of the presented topics. Incoming president P.D.S. Lee from Seoul, Korea, now leads the International Society for Behçet's Disease, and it is anticipated that this organization will continue to promote studies in the disease, with a focus on randomized controlled trials to prove drug efficacy, as well as multidisciplinary and international approaches to pathophysiological, epidemiological, and clinical topics. The 14th International Congress on BD will be held in London, UK, in 2010.

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