



Ettal Workshop



Organised and chaired by professors M. Zierhut (University of Tübingen, Germany) and S. Ohno (Hokkaido University, Japan) a two-day workshop on "Immunology of Behçet's Disease" was held in Ettal (Bavaria-Germany) on October 12 and 13, 2000. There were about 40 participants, 25 of whom gave formal papers. Even though the main heading was immunology many aspects of BD were discussed including epidemiology and treatment. One scientific highlight of the meeting was the papers and the related discussion about the new transgenic animal models including the transgenic HLA B51, MICA and HLA B51+MICA. However neither the basic science or the clinical students of BD found the clinical findings or the immunological/propensity to inflammation characteristics of these animal models entirely satisfactory. Another highlight of the meeting was the treatment of severe eye disease by TNF-alpha blockage as presented by S. Ohno. Even the numbers treated were rather small; the results were quite promising.

The social side was superb. Held in a beautiful monastery on the Bavarian mountains our hosts (Department of Ophthalmology at Tübingen University) were most accommodating. Evidently a scientific publication related to this meeting is also in the horizon.

Preparations for the 10th International Conference on Behçet's Disease

Christos C. ZOUBOULIS

President, The 10th International Conference on Behçet's Disease

The 10th International Conference on Behçet's Disease will be held in Berlin on 27 -29 June 2002 and is the first thematic conference to be organized under the auspices of the currently inaugurated International Society of Behçet's Disease.

Venue of the Conference will be the University Medical Center Benjamin Franklin of the Free University of Berlin at Steglitz, a southwestern suburb of the city. Plenary and concurrent sessions as well as a poster exhibition will increase the number and interest of active participants. Most sessions will be thematically organized. There will also be selected invited lectures of international experts, satellite therapeutic symposia and an industrial exhibition. Our purpose is to construct a scientific program with high impact providing current information on clinical subjects and research on this multisystem disorder.

On the other hand, we try to keep the participant expenses as low as possible in order to attract young scientists and students working or wishing to work in this interesting clinical and scientific field in the future. The early registration fee (before February 28, 2002) is 420 German Marks with a reduced fee for members of the International Society of Behçet's Disease of 370 German Marks. The late registration fee (from March 1, 2002) and on site registration costs 550 German Marks; the members of the International Society of Behçet's Disease paying 500 German Marks.

Over 800 clinicians and scientists are going to receive the first announcement of the Conference in the next days.

The medical conference will take place simultaneously with the 2nd International Convention for Patients with the Silk Route Disease (Behçet's Disease) giving for the first time the opportunity for physicians and patients all over the world to communicate directly. The early registration fee (before February 28, 2002) for patients-participants at the the 2nd International Convention for Patients is 350 German Marks and the late registration fee (from March 1, 2002) and on site registration costs 450 German Marks.

The deadline for the submission of abstracts is February 28, 2002.

Registration to the Conferences is easy. The abstract form, the registration form, all information about hotels and reservations, details for the cultural and social program as well

BD NEWS

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We are very happy to announce that Prof. Shigeaki Ohno and Dr. Tomomi Nishida have accepted to join us as associate editors starting with the next issue of the BD News. H. Yazici - Y. Tüzün

as further information is to be found on the website <http://userpage.fu-berlin.de/~zoubbere/> which will be updated on a continuous basis.

On the threshold of the new millennium Berlin is an exciting cultural and cosmopolitan center in the heart of Europe. You can study the past, enjoy the present and look at the future unfolding in front of your eyes. Participants and accompanying persons will experience a program which will provide the opportunity of getting a strong impression of the variety of the new capital of Germany. Historical expeditions, cultural events and trips through the new quarters of the city will show you the kaleidoscope of an exciting place. The conference takes place in a period of the year when the weather can be expected to be nice and sunny.

For further information please contact the RKM Konferenzmanagement at RKMCR@aol.com

Important Notice: ISBD will grant up to eight, 500 dollar bursaries to young investigators (aged 35 years or less) submitting abstracts to the 2002 Berlin Meeting. The congress registration fee will also be waived from the winners of these bursaries who will be selected by a peer-review process.

For application, please send a brief letter of intent, which includes your date of birth, with your abstract. The deadline for abstract submission is February 28, 2002.



Neurological Involvement in Behçet's Disease

By Aksel SiVA (Turkey)

One of the many systems to be involved in Behçet's disease (BD) is the nervous system. The reported range for the frequency of neurological involvement has been 2.2 - 49 %. This rate does not exceed 5 % in large series. We have found that the mean age of onset for BD and neurologic involvement were 26.7 (8.0, and 32.0 (8.7 years respectively in our patient population, similar to other reports.

Neurological involvement in BD occurs more commonly in males.

Patients with BD may present with different neurological problems, related either directly or indirectly to the disease. Central nervous system (CNS) involvement secondary to vascular inflammation, cerebral venous (dural) sinus thrombosis, the Neuro-Psycho-Behçet variant in which an organic psychotic syndrome is prominent, are direct effects and are designated as "Neurobehçet Syndrome" (NBS). Tension type headache, depression and neurologic complications of BD treatments are among indirect neuro-psychiatric consequences of the disease. Peripheral nervous system involvement is extremely rare. However neurophysiological studies may demonstrate non-specific findings in some patients.

Clinical features: The most common neurological symptom among patients with BD is headache. Some patients with BD report a paroxysmal migraine-like pain, which is bilateral, frontal, of moderate severity and throbbing. This type of headache generally starts after the onset of the systemic findings of BD, and may be seen during exacerbations of systemic findings such as oral ulcerations or skin lesions, though this is not always the rule. This non-structural headache of BD commonly is not associated with primary neurological involvement. However, a substantial number of patients with BD may report a severe headache of recent onset, not consistent with a co-existing primary headache or ocular inflammatory pain. These patients require further evaluation even if they do not have neurological signs, as this headache may indicate the onset of NBS. In addition to headache alone, NBS may present with focal or multifocal CNS dysfunction with or without headache. The most common symptoms detected at onset in patients with BD besides headache are; weakness on one side of the body (hemiparesis), or both legs (paraparesis); brainstem and cerebellar symptoms such as double vision, dysarthria, facial weakness, tremor and gait instability; and to a lesser extent cognitive and behavioral symptoms. Rare presentations include isolated optic neuritis, psychiatric manifestations referred to as neuro-psycho-Behçet Syndrome, epilepsy, aseptic meningitis, intracerebral hemorrhage due to ruptured aneurysms, extrapyramidal syndromes and peripheral neuropathy.

Clinical and neuroimaging evidence confirm that NBS can present with a variety of neurological symptoms and display findings which may be subclassified in two major forms. One is due to small venous disease and causes the focal or multifocal CNS involvement manifested in the majority of patients (CNS-NBS or intra-axial NBS). The second form is due to cerebral venous sinus thrombosis (CVT or extra-axial NBS), which has more limited symptoms, a better prognosis and generally an uncomplicated outcome. Some authors consider to designate only CNS parenchymal involvement as NBS, and include cerebral venous sinus thrombosis within the spectrum of so called vasculo-Behçet. However, as both have neurological consequences, we favor to identify them as "intra-axial NBS" and "extra-axial NBS", respectively. These two types of involvement occur in the same individual very rarely. We have not observed such a combination in our patient population. These two forms of NBS presumably have a different pathogenesis. Many of the CNS-NBS patients with small vessel inflammation have a relapsing-remitting course initially, with some ultimately developing a secondary progressive course later. A few CNS-NBS patients will have a progressive CNS dysfunction from the onset. Patients with CVT, are more likely to experience a single uncomplicated episode and rarely further episodes of intracranial hypertension.

As patients with CNS-NBS are young and present with an acute or subacute brainstem syndrome or a hemiparesis, their disease may be mistaken for multiple sclerosis or stroke of young onset, especially in the absence of the systemic signs and symptoms of BD. Notably, we have observed that in most cases with BD who present with neurological manifestations a careful history will reveal either the presence or a past history of recurrent oral ulcerations with or without other systemic findings of the disease. Furthermore neuroimaging is highly suggestive of NBS.

Neuro-imaging: Neuro-imaging studies in CNS-NBS have shown that cranial magnetic resonance imaging (MRI) is both specific and more sensitive than computerized tomography in demonstration of the typical reversible inflammatory parenchymal lesions. Lesions are generally located within the brainstem, occasionally with extension to the diencephalon, and basal ganglia at the base of the cerebral hemispheres. Hemispheric lesions within the periventricular and subcortical white matter are not common. MRI/MR-venography is highly sensitive in demonstrating CVT.

Cerebrospinal Fluid (CSF): If performed during the acute stage, CSF studies usually show inflammatory changes (i.e. increased cells and an elevated level of protein) in most cases of CNS-NBS. CSF in patients with CVT may be under increased pressure, but the cellular and chemical composition is usually normal. An inflammatory CSF usually indicates a bad prognosis.

Treatment: Neurological involvement in BD is heterogeneous and it is difficult to predict its course and prognosis, and response to treatment. Acute attacks of CNS-Neuro-Behçet syndrome are treated with either oral prednisolone (1mg/kg for two weeks) or with high dose intravenous methyl prednisolone (IVMP-1g/day) for 5-7 days. Both should be followed with oral tapering over two-three months in order to prevent early relapses. Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, immunomodulatory agents such as interferon- α and, more recently thalidomide have been shown to be effective in treating some of the systemic manifestations of BD, but none of these agents have been shown beneficial in CNS-NBS in a properly designed study. Cyclosporine was reported to cause neurotoxicity or to accelerate the development of CNS symptoms and therefore its use in NBS is not recommended. Cerebral venous sinus thrombosis in BD is treated with a short course of steroids sometimes with the addition of anticoagulation. Long term prophylactic treatment is not warranted in these patients, as recurrences are uncommon.

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A Critical Clinicopathologic Evaluation of Nodular Lesions of Behçet's Disease

By Cuyan DEMİRKESEN and Cem MAT (Turkey)



Approximately 50 % of BD suffer from nodular lesions mostly located on the lower extremities. These nodules are painful, erythematous or violaceous in colour, measuring 1 to 8 cm. in diameter. They usually have an acute onset and heal with hyperpigmentation. The nodular lesions of BD are either superficial thrombophlebitis (ST) or erythema nodosum (EN)-like lesions. Although clinical differentiation of these nodules is not always easy, ST is frequently located on the medial side of the legs along the veins. ST is highly associated with deep vein thrombosis in BD. Reports about the nature of the EN like lesions in BD have been conflicting. Some authors indicated these lesions resembled EN both clinically and histologically, while others have reported findings of neutrophilic vasculitis. Therefore, we attempted to evaluate the histologic features of these lesions with control groups, composed of two common types of panniculitis, EN and nodular vasculitis (NV). Nodular lesions of 24 BD, 20 EN and 25 NV patients were compared according to a check list of histologic parameters by two observers in a masked manner. Biopsies of the nodular lesions of BD were obtained from volunteer patients who fulfilled the criteria for complete BD and attended a dedicated BD outpatient clinic in Cerrahpaşa Medical Faculty. Nodular lesions due to ST were excluded. Later on, the frequency of each histologic parameter for each disease category was compared by constructing frequency distribution graphs. Neutrophilic vasculitis was noted in 43 % of nodular lesions in BD. A neutrophil predominating inflammatory cell infiltrate was also a statistically important parameter in favour of BD when compared to NV and EN. This finding supports the earlier observations that EN-like lesions of BD are neutrophilic vascular reactions as papulopustular and pathergy lesions also are. Furthermore, it can be speculated that the lymphocyte predominating reaction in subcutis, noted in some BD, might be following a neutrophilic vascular reaction during the evaluation of these lesions, as proposed for pustular lesions of BD. Although the involvement of veins were seen more often in BD compared to EN and NV, the calibre of the involved vessels were mostly arterioles and venules. Necrosis, necrobiosis and granuloma formation in the subcutis was less frequent.

Although the diagnosis of BD is usually not established on the basis of histologic features detected in nodular lesions, we wanted to find out if there were any distinguishing features differing from EN and NV. Therefore, a paired t-test was done on frequencies of the 20 histological parameters taken as a group in BD vs NV, BD vs EN and NV vs EN. The histologic features detected in the nodular lesions of BD were akin to NV than EN. As a result, there was no significant difference between BD and NV. This, in turn suggests that the nodular lesions of BD may indeed be due to vasculitis as in NV. On the other hand, there was a significant difference between BD and EN ($p=0.005$). Presence of septal panniculitis, lymphocyte predominating infiltrate, absence of many vascular changes, as well as necrosis were features in favour of EN. We now consider that the histologic features of the nodular lesions of BD have enough specificity to differentiate them from EN associated with other diseases.

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Epidemiology of Adamantiades-Behçet's Disease

By Christos C. ZOUBOULIS (Germany)

Adamantiades-Behçet's disease is a universal rare disorder with varying prevalence. It occurs endemically in the Eastern Mediterranean area and in Central and East Asia. The spread of these geographic areas along the old silk route and associated immunogenetic data support the hypothesis of distribution through the immigration of old nomadic tribes. Transfer of genetic material and/or of exogenous agent(s) may have been responsible for the expansion of the disease.

Prevalence

The highest prevalence of the disease has been reported in Northeastern Turkey (370 patients per 100,000 inhabitants), while the overall prevalence in Asia is 20- to 30-fold lower and in Europe and the U.S.A. more than 150-fold lower. Single or a few cases have been reported in all continents.

In countries with several ethnic populations, certain ethnic groups are mainly affected. In Taiwan, all 103 patients diagnosed between 1970 and 1988 were Chinese. In Iran, Turks presented a significantly higher prevalence than Caucasians and Semites, while no patient was found among Zoroastrians, who are isolated-living Caucasians. In Kuwait, Kuwaiti Bedouins were not affected, whereas 1.35:100,000 non-Arab Kuwaiti were diseased. In Berlin-West, the prevalence among Turks was 20.75:100,000 inhabitants of Turkish origin compared to only 0.42:100,000 Germans in 1989.

In ethnic populations the prevalence of the disease seems to be strongly dependent on the geographic area of their residence. The prevalence in Turks was calculated to decrease up to 18-fold by moving from Eastern Turkey to Germany. The prevalence of the disease in Japan decreased up to 30-fold by moving from northern to southern Japan and was annihilated in Japanese living in Hawaii and in the U.S.A. These data indicate that environmental factor(s) possibly trigger(s) the onset or the development of the disease in genetically determined populations.

Long-time studies have found a throughout increasing prevalence, which may be due to the chronic character of the disease. In Japan, there were 6.3-8.5 patients per 100,000 inhabitants in 1972 and 13.5:100,000 in 1991. In Berlin-West, 0.65 patients per 100,000 inhabitants were detected in 1984 and 2.26:100,000 in 1994. In Rome, Adamantiades-Behçet's disease was found responsible for 3% of uveitis cases between 1968 and 1977, but for as much as 7.5% between 1978 and 1987.

Incidence

Data on the incidence of the disease are sparse and ambiguous. In Japan, a country with well organized registration of patients with Adamantiades-Behçet's disease, 0.89 new cases per 100,000 inhabitants have been diagnosed in the year 1984. In 1990, 0.75 new cases:100,000 have been registered indicating the reaching of a plateau after a rapid increase of incidence since 1972. In Taiwan, 5 patients/year visited 6 major medical centers for the first time from 1979 to 1983 and 14 patients/year from 1984 to 1988.

Age of Onset

The disease usually occurs around the third decade of life. An average age of onset of 31.7 years was recorded in East Asian countries, 26.5 years in Arab countries, 25.6 years in Turkey, 19.9 years in Israel, 25.9 years in Europe and 28.3 years in the Americas. Cases of early and late onset have also been reported (months to 72 years). Juvenile disease was estimated in France to be 0.17 patients per 100,000

inhabitants and reported in 1.5 to 20.8% of patients in different countries.

Sex Distribution

In contrast to old reports about androtropism, current studies register an approximately equal male-to-female ratio in several populations. Androtropism is still observed in Arab countries, while gynaecotropism is evident in some northern European countries and in the U.S.A.. Japanese studies has shown that there is a real increase in the numbers of female patients which is associated with a trend towards a milder disease.

Familial Occurrence

Familial occurrence is more frequent in Korean (15.4%) than Japanese or Chinese (2.2-2.6%) families ($p < 0.001$). Also Arabs, Israeli and Turks presented higher frequencies of familial cases (2.0-18.2%) than Europeans (0.0-4.5%; $p < 0.001$). Juvenile patients exhibit higher familial occurrence rates than adult ones.

Onset Manifestations

Oral aphthous ulcers represent the onset feature of the disease in the majority of the patients worldwide (47-86%). Genital ulcerations (0-18%), skin lesions (0-27%) - especially erythema nodosum (0-19%) -, ocular lesions (0-35%), arthropathy (0-24%), neurological features (0-12%) and vascular involvement (0-3%) can also occur as onset lesions. The high frequencies of mucocutaneous and ocular lesions as onset lesions confirm the importance of these clinical features for diagnosis. Highly recurrent oral aphthosis is a warning signal for Adamantiades Behçet's disease. Fifty-two per cent of 67 prospectively evaluated patients with recurrent oral aphthosis (in average 10 recurrences per year) in Korea developed Adamantiades Behçet's disease in 8 years after development of oral aphthous ulcers.

Clinical Findings

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 features of the disease. Sterile pustules (28-66%) and erythema nodosum (15-78%) are the most frequent skin lesions. A positive pathergy test has been reported in 6-71% of the different patients groups. Lower rates of positive pathergy test were assessed in European, U.S. American and Brazilian patients (32%) than in patients in the rest of the world (54%, $p < 0.001$) and higher rates of arthropathy in Europeans, U.S. Americans and Brazilian (62%) than in the latter group (41%; $p < 0.001$). Gastrointestinal features were assessed more frequent in Japanese and European (16%) than in Korean and Turkish patients (3%, $p < 0.001$). Ocular lesions in south-eastern European patients (Italian and Greek) were significantly more common than in south-western as well as northern European patients.

HLA-B51 Association

HLA-B51 is significantly associated with Adamantiades-Behçet's disease. However, none of the functional correlates appear to be restricted by HLA-B51. Current evidence indicates that HLA-B51 is not involved directly in the etiology of the disease but might be closely linked to disease-related gene(s). On the other hand, HLA-B51 was found to be a marker for unfavorable prognosis, especially for an earlier development of the disease, for ocular lesions and vessel involvement. HLA-B5-positive German individuals as well as from other northern European countries were detected to present a lower relative risk for the disease compared to southern Europeans. The relative risk of HLA-B51 individuals for the disease does not follow the world-wide distribution of HLA-B51; it is increased in a small geographic area which well correlates with the major trade routes of the antiquity.

Course and Prognosis

Adamantiades-Behçet's disease is usually diagnosed with a delay of 1-15 years after the appearance of the first symptom. The disease exhibits a potentially severe course with mortality rates of 0 to 6.3%,

mostly involving male patients. The real increase of female cases in Japan are associated with a decrease of the mortality rate, namely from 1% in 1972 to 0.4% in 1991. Central nervous system, pulmonary as well as large vessel involvement and bowel perforation are the major life-threatening manifestations. Blindness and the consequences of central nervous system involvement are the most disabling features. There is evidence that a lethal outcome is often due to delayed diagnosis and treatment. HLA-B51 positivity, male gender and early development of systemic features are considered markers of severe prognosis. Spontaneous remission of certain or of all manifestations have been observed in a part of patients several years after the onset of the disease.

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