Foreword

By Hasan YAZICI & Yalçın TÜZÜN (Turkey)

BD Newsletter aims to be the official organ of communication for the International Society for Behçet's Disease. Its reader target is, for the time being, only the physicians. On the other hand we plan to have adequate space for a patient forum, thus also a patient reader audience, for this Newsletter once we, with luck, secure more funding.

Our Newsletter is currently scheduled for biannual publication. Our sincere thanks go the journal, The Clinical Experimental Rheumatology, Pisa- Italy, the editorial office of which will edit and print our Newsletter, free of charge for the first 4 issues.

You will find in this first issue mainly viewpoint - state of the art articles, all solicited, from a group of international experts on various aspects of BD. So we are a bit "stuffy" for starters. However we wish eventually that this Newsletter becomes a bulletin board of what is hot, what is new and what our colleagues and patients want other colleagues and patients to hear.

Finally our congratulations go to Prof. S. Lee (President) Prof. D. Bang (General Secretary) and all others involved in the organisation of our 9th International Conference (Seoul, May 27-29, 2000) during which this Newsletter will be distributed for the first time.

Editors

International Society for Behçet's Disease (ISBD)

By Colin BARNES (U.K.)

The first international conference on Behçet's Disease (BD) was held in Rome, Italy in December 1964. However, the development of a regular series of International Conferences on BD can be attributed to Professor Nihat Dilsen who organised such a conference during the Istanbul Medical Convention in 1977. This was followed by similar conferences in Tokyo (1981), London (1985), Mayo Clinic (1989), Paris (1993), Tunis (1996) and Reggio Emilia, Italy (1998), and the forthcoming one in Seoul (May 2000). The increase in interest in BD is demonstrated by the progressive reduction of the interval between International Conferences from four to two yearly and also by the inauguration of the new ISBD in Seoul.

In Tokyo in 1981 an informal discussion led to the suggestion that an International Study Group for BD (ISGBD) should be formed which took place in London in 1985. This group has enlarged currently being 29 colleagues from 19 countries representing 7 medical specialities. The members of the ISGBD have remained in contact over the years largely through the International Conferences. However, as a result of the increasing interest and research activity in BD internationally there was a request for a substantial number of new members which lead to the decision that an ISBD, with a

wide membership, should be formed. The aim of the new ISBD would the broad one "to extend and communicate knowledge about BD". Inter alia this is likely to include; continuation conferences; co-ordination of research activities on an international basis while also aiming to support the individual researcher; to promote the formation of specialist working groups; to produce a newsletter; to promote, acknowledge and support research in BD, good clinical practice, CMD and teaching activities in BD; and finally to represent the interests of BD to other professional, scientific, representative and international bodies.

In the following two years a constitution was drafted which, after discussion, was amended and agreed in Reggio Emilia in 1998. This led to the nomination of an interim Acting Secretary, Advisory Committee and Council the latter being the current ISGBD. They were given the tasks of inviting applications for membership, organising the election of the first officers and council, and organising the formal inauguration of the ISBD.

At the time of writing 133 applications for full membership have been received from 25 countries representing 16 medical specialities, and one for associate membership from a representative of a patient group. It has been arranged that elections for the positions of President, President-elect and Vice-President will be held at the forthcoming International Conference in Seoul in May 2000. It was agreed, in the drafting of the constitution, that the President should nominate the Honorary Secretary and Treasurer to facilitate communication. At the same meeting the first General Assembly of Members will be held at which the ISBD will be formally inaugurated, the election of officers will be confirmed, and the Council will be elected.

Therefore, it is hoped that from May 2000 the study, research activities, education and communication, awareness and management of BD will take a further step forward.

"The First International Convention For Patients With Silk Road Disease", 19-22 May, 2000 Yokohama, Japan

Another very important organisation for both research and patient care in BD will have taken place just before the 9th International Conference. It is being organised by the Yokohama City State University Medical School, Department of Ophthalmology in conjunction with the National Behçet's Syndrome Association of Japan. Executive director of this convention is Dr. T. Nishida, who works with Prof. S. Ohno.

Being the first of its kind the organisers are hoping that their attempt will provide a good platform for patients from many different parts of the world to discuss their problems both among themselves and with their physicians, suggest solutions and be informed about current BD research and management. The program includes formal lectures as well as many discussion groups and joint sightseeing.

The patient participation to this convention will be mostly sponsored and the main sponsors are the Research Foundation of Ocular Disease in the Elderly, Japan, Japanese Ministries of Welfare, Education and Foreign Affairs, Kanagawa Prefecture, Yokohama - City and the National Council of Social Welfare of Japan.

Behçet's Disease or Behçet's Syndrome:

-Considerations for the Unified Diagnosis Related Terminology-

By Sungnack LEE (Korea)

The clinical manifestations of what is known today as Behçet's disease were described in as far back as the era of Hippocrates. However, in 1937, the Turkish dermatologist Hulusi Behçet was the first to give a comprehensive description of the symptom-complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis as a disease entity, which today bears his name.

During the last six decades, more than 4,500 references related to Behçet's disease were published (1998).[1] It reflected results of the strong research activities and the worldwide interest in this unique disease. However, we Behçetologists have not yet found a consensus for a unified terminology. In other words, we have used different medical terms to describe this condition such as Behçet's disease, Behçet's syndrome, or others for nearly sixty years.

In fact, the difference occurred mainly due to a single matter: whether to use the term "Syndrome" or "Disease".

To reach an agreed terminology, the author's group reviewed a list of published papers from the past sixty years that had used medical terms like syndrome or disease for Behçet's condition.

The Ophthalmotogist T. Jensen (1941)[2] had confirmed Behçet's observations through his clinical case report, and he became the first author to mention the terminology <Syndrome Behçet> in his publication. In 1954, G. Lemke first used the term <Behçet's Disease> (Behçet'sche Krankheit).[3] Since that time and until today, we have been using both terminologies synonymously: Behçet's syndrome and Behçet's disease.

According to our studies, among 2,228 publications related to Behçet's condition over the past sixty years, 1,591 papers used the term "disease" in the title (71.40%) while 637 used the term "syndrome" (28.59%).

Furthermore this was a time related phenomenon. Among the 112 publications between 1941 and 1969 the term "disease" was used in slightly less than half (47%) of the cases. However this percentage rose up to 82% among 986 articles published between 1990 to 1998.

Recently we sent out survey questionnaires to 34 board members of the International Study Group for Behçet's Disease. Although the total number of respondents was relatively limited, the professional qualities of our respondents were highly sophisticated so that the significance of the responses could be highly valued.

Of the 34 questionnaires, which were sent, 22 responses were collected:

The first question was: Should we have an agreed terminology regarding the Behçet's-condition? Yes: 21/23 responders (91.30 %); No: 2/23 responders (8.69%)

The second question was: Which terminology is commonly applied in your country? Behçet's syndrome: 3/23 (13.04 %); Behçet's disease: 15/23* (65.21%); Both: 4/23 (17.39%)

The third question was: Which terminology do you prefer personally? Behçet's syndrome: 8/23 (34.78%); Behçet's disease: 14/23* (60.86%); Both: 1/23 (4.34 %)

* One responder used the term Admantiades-Behçet's disease. Since our survey's purpose was to know whether the term disease or syndrome should be applied to the Behçet's condition, the mentioned case was included with the term "disease"

The respondents presented some remarkable comments.

- No one could ever die of a syndrome. Since patients with Behçet's condition could die or go blind, Behçet's condition must be a disease (J. D. O'Duffy).
- The entity should be separated as Behçet's disease for Silk Route people and Behçet's syndrome for others (George E. Ehrlich).
- One of the respondents mentioned that we had already agreed at one of the International Meetings to use the term Behçet's disease (T. Lehner).
- We should also differentiate the various disease manifestations eg. Ocular-Behçet's disease, Neuro-Behçet's disease, etc (D. BenEzra).
- As it has been observed in the Western countries and inside the Silk Route, Behçet's disease may include various subtypes. One of the respondents believed that it is also true for other diseases such as rheumatoid arthritis, and systemic lupus erythematosus. In the latter disease, individual patients express different phenotypes even in the same country. Nonetheless, we have never called them RA syndrome and SLE syndrome, respectively. In addition, the same HSP-peptide could cause Behçet's disease irrespective of inside and outside the Silk Route. Therefore, he enthusiastically claimed that Behçet's disease should be termed "Behçet`s disease", but not "Behçet's syndrome" (T. Sakane)

In conclusion our study group firstly suggests that it is time to come to an agreed consensus for a unified terminology.

Our study group further suggests that, based on the findings of the different studies, all of us, as Behçetologists should declare to use only one diagnostic terminology: Behçet's disease.

Our general image as Behçetologists without a defined diagnosis related terminology could not be viewed favorably by the whole medical world. We should seriously concern the fact that we do not even have an agreed diagnostic terminology yet.

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Treatment of Behçet's Syndrome

By Sebahattin YURDAKUL &
Vedat HAMURYUDAN (Turkey)

Current treatment of Behçet's syndrome (BS) still continues to be symptomatic and empirical but most would agree that the outcome of our patients is better today than it was 20-30 years ago. Although the available agents used in the treatment of BS remain almost (with the exception of

alpha-interferon) unchanged during the last two decades, we use them with more skill these days and most of that skill comes from information obtained in clinical trials.

There is still considerable difference even among the experts in their approach to the treatment. A survey, which was conducted in the last International Congress in Reggio Emilia, has demonstrated the lack of consensus on the controversial issues of treatment.[1] Another example to this marked divergence is reflected in a recent review on BS.[2] In this review, colchicine has been recommended for preventing both anterior and posterior uveitis with a high degree of efficacy whereas the authors of this letter would hardly prescribe colchicine to their patients for the treatment of uveitis. We believe that these differences will continue until we know more about the pathogenesis, until more properly conducted drug trials are available and until we define reliable instruments for assessing disease activity and damage.

The treatment in Behçet's syndrome is tailored to the site and severity of disease manifestations. Mild orogenital ulcers are treated with reassurance and local application of steroids and anaesthetics. On the other hand we know that male patients and those with a young age of onset (<25 yr.) generally have more severe disease course and require more aggressive treatment.

It is worth underlining that of the many currently used agents for the treatment various manifestations of BS only some (namely azathioprine, cyclosporine, thalidomide, colchicine and IF-α) have been shown to be beneficial in controlled clinical trials.

Of these drugs thalidomide has a prompt and powerful effect on oral and genital ulcers along with follicular lesions of BS. Additionally, it is the only drug that can induce complete relief of oral and genital ulcers.[3] However, it does not seem to be a disease-modifying drug and relapses are seen after stopping treatment. Because of its severe side effects like teratogenecity and polyneuropathy, this drug should not be used routinely in the clinic. Until safe analogues of this drug are available, thalidomide should be reserved for severe cases resistant to other alternatives.

Interferon alpha, alone or in combination with low dose steroids, might be a powerful alternative for severe eye involvement of BS.[4] Various studies have also reported its efficacy in the treatment of mucocutaneous and joint manifestations of BS. The effect of interferon starts relatively early but relapses usually come after stopping treatment.
It is worth mentioning here that an infectious etiology has been claimed for many years and various strains of streptococci have been in the forefront. A trial of penicillin from Ankara has already indicated promising outcomes especially in mucocutaneous disease and arthritis[5] but clearly more work needs to be done.
An additional issue to be addressed in treatment is that of combination therapy. Although many centers use several drugs in combination (like colchicine with an immunosuppressive or azathioprine in combination with cyclosporine), there is precious little formal data on such treatment. This sort of formal experience is also definitely needed for better patient management.

In summary, recent years have seen substantial progress in the treatment of eye involvement and mucocutaneous manifestations of BS. Unfortunately we are still far from satisfactory in the treatment of life threatening manifestations of BS such as central nervous system and vascular involvement. Multi-center studies and improved methods in assessing patients will help to improve treatment of this mysterious disease. We hope that our newly formed International Behçet Society will be instrumental in the organization of such multicenter studies.

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Developing a Disease Activity Index

By M. Anne CHAMBERLAIN
& Alan TENNANT (U.K.)

The Behçet's Disease Activity Form is now in widespread use. At the recent meeting discussions about its use led to considering the desirability of a Behçet's Disease Activity Index (BDAI) derived from the form. This task was given to the Rasch Studies Centre (RSC) in the Rheumatology & Rehabilitation Research Unit at the University of Leeds in the UK. At the meeting a request was made for contributions of data to the analysis and to-date four countries have donated data.

The basic requirement for measurement laid down by the RSC was for a set of symptoms which could be summated to provide a simple index of severity. With both physicians' and patients' overall severity scores available such an index should clearly discriminate across these summary measures. An Index should also be free from Differential Item Functioning (DIF) by age and gender, and most important by country. What this means is that the probabilistic relationship between any proposed set of items should hold constant across countries.

The approach used is that of Item Response Theory (IRT) which is a general statistical theory about item (symptom) and scale performances and how that performance relates to the levels of disease activity.

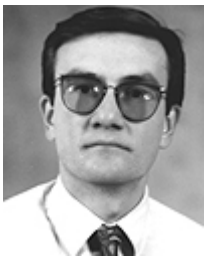
The data from 242 patients have been analysed for the first stage of this exploratory analysis. With a mean age of 37 years, 47% were male and the mean perception of disease activity of patients and clinicians being 3.89 and 3.32 respectively on a simple 1-7 scale (smiley faces). The most common symptoms reported were mouth ulcers (68%), fatigue (46%), joint arthralgia (36%), headaches (36%) and eye problems (26%). There were some significant variations in prevalence between countries. For example, Skin Lesions (EN/ST) were reported by 13% of patients in Korea, but 53% of patients from China. Headaches were common in the UK (71%), but rare in Korea (15%). These variations cause problems with the basic requirement of a consistent probabilistic relationship across countries.

Perhaps surprisingly therefore, 16 symptoms did maintain such an order. These included mouth ulcers, joints arthralgia, joints arthritis, any red eye or painful eye, balance loss, arm pain/swelling and breathlessness. The symptom leg/pain swelling was the least commonly reported problem in this set of 16, arguably the upper level of severity.

However, this finding might be modified if a larger data base were available, as some impairments on the BDAF were not represented in the data analysed. Mouth ulcers were the most common and thus can be considered to mark the lowest level defined by adequate fit to the one parameter IRT (Rasch) model. DIF was largely absent, although skin lesions (pustules) did show some variation by country. The sixteen item scale showed strong discrimination across both patients' and physicians summary scales of disease activity (Mann Whitney U, $p<.001$). For example, an average score of 0.6 was found for the most smiley face for patients, compared to 6.3 for the most miserable face.

In summary a 16 item (symptom) scale has been identified which appears to offer a unidimensional scale for disease activity, which is largely free of DIF and discriminates across self- of physician reported disease activity states. A second set of data is currently being collected to independently validate these results.

Behçet's Disease: What's new related to pathogenesis?



By Haner DIRESKENELI (Turkey)

Vascular injury

Vascular involvement in BD is predominantly venous in contrast to SV. The rare presence of pulmonary emboli is suggestive of a "sticky" thrombi and in histopathological studies, in addition to thrombi, inflammatory infiltrates in vessel walls point to a vasculitic process. Antibodies against endothelial cells (AECA) have been described in BD, but specific target antigens of AECA, such as adhesion molecules, proteoglycans or co-stimulatory molecules (as recently described CTLA-4 of anti-lymphocyte antibodies) are still unknown. Increased Factor V Leiden mutation, mainly in patients with venous thrombosis and retinal occlusive disease also show the role of increased propensity to thrombosis in BD.

Immune effector mechanisms

Th1/Th2 balance is suggested to be critical in the induction and regulation of autoimmunity and inflammation. A Th1 type; IL-2, IFN-γ and IL-12 dominant cytokine profile is present in active BD, whereas Th2 activity (IL-4, IL-13), except for IL-10, is controversial. A pro-inflammatory mileu with serum and local elevations of monocyte-macrophage derived cytokines such as IL-1β, IL-6, TNF-α and chemokines such as IL-8 and MCP-1 is also demonstrated. This profile might be responsible for the increased O_2 release, enzymatic activity, phagocytosis and chemotaxis of neutrophils, reported by some denied by others.

An infectious etiology

Although herpetiform ulcers are not common, Herpes simplex virus (HSV) is currently the only virus possibly associated with BD. HSV DNA has been demonstrated in the genital and intestinal ulcers of BD patients and HSV infection increases T lymphocyte adhesion to endothelium. Thirty percent of ICR mice inoculated with HSV developed Behçet's disease-like symptoms.

Among bacterial agents mainly streptoccocci have been implicated. A Th1 type cytokine response and increased $\gamma\delta$+ T cells are observed after *in vitro* streptococcia stimulation of BD lymphocytes. Cytokine responses against *St. salivarius* are suppressed by minocyline treatment.

Molecular mimicry and 65 kD HSP

65 kD heat-shock protein (HSP) is a candidate antigen of streptoccocal infection in BD. Studies with mycobacterial 65 kD HSP which has >90% homology with streptoccocal HSP and its 60 kD human homologue have shown increased T cell and humoral responses to HSPs in patients from UK, Japan and Turkey. BD patients with uveitis, in addition to streptoccocal and human HSPs, also have increased antibody responses to retinal HSP, suggesting a *cross-reactivity* of these antibodies. Mucosal or systemic inoculation of human 60 kD HSP immunodominant epitope 336-51 causes uveitis in rats. In contrast to the situation in BD, T cell responses to human 60 kD HSP are thought to be protective in autoimmune diseases such as juvenile rheumatoid arthritis and further characterization of HSP responsive T cells, such as their Th1/Th2 cytokine profile, is required.

Superantigens and hyperreactivity

In addition to streptoccocal antigens, Escherichia coli and Staphylococus aureus also activate BD lymphocytes to release increased amounts of IFN-γ and IL-6. A further observation of increased IFN-? response of Behçet's T lymphocytes to very low (1-10 pg/ml) doses of staphyloccocal superantigens SEB and SEC1 is proposed as an evidence of T cell hyperreactivity in BD, which might relate to abnormalities in signal transduction triggered through the T cell receptor. A broader intra-cellular signaling abnormality of all immune cells (including neutrophils) which lowers the threshold of inflammatory responses to external stimuli, as proposed for familial Mediterranean fever with decreased pyrine expression of neutrophils, might also be an interesting hypothesis.

γδ+ T cells, found to be increased both in peripheral blood and tissue infiltrations, can also be a part of this antigen non-specific immune activation. In addition to conventional peptide antigens such as HSPs, γδ+ T cells recognize non-peptidic small molecules and activate polyclonally after infections, giving them a role close to *innate immunity*.

Organ-specific antigens

Immune responses to organ-specific antigens such as dermal keratins in psoriasis, collagen type II in rheumatoid arthritis or retinal-S antigen in uveitis were previously demonstrated. Similarly, different organ-specific antigens might be relevant for BD subgroups with muco-cutaneous, vascular or articular involvement such as mucosal, endothelial or synovial antigens. HLA-B derived, uveitogenic peptide 125-38 might be an example of these organ-specific antigens in BD. These need further scrutiny.

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A Journal within a Journal

Prof. S. Bombardieri, the Editor in Chief of Clinical and Experimental Rheumatology offers the Behçetologists, a common, a respected site and us for some of our future scientific publications. He proposes to have an annual supplement of this journal be devoted entirely to original and review articles as well as case reports related to Behçet's disease and Familial Mediterranean Fever. This supplement will be peer-reviewed and your scientific contributions will be covered by all the major source indexes, including the Science Citation Index and the Current Contents.

BD NEWS

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