

**The 13th International Conference on Behçet's Disease**  
**Pörschach, Austria, 24–27 May 2008**

The 13th International Conference on Behçet's Disease was attended by more than 160 delegates, and 138 abstracts were presented orally or as posters.

### **Neuro-Behçet's**

Professor Adnan Al-Araji from Stoke in the UK gave an overview of central nervous system involvement in Behçet's disease. The reported incidence of neuro-Behçet's varies around the world, but overall it seems that around 10% of BD patients will develop it. Neuro-Behçet's can be classified into parenchymal and non-parenchymal types. The former involves the brain stem and central areas of the brain and spinal cord and represents about three-quarters of cases, while the latter mainly manifests as intracranial hypertension. Only about 10% of cases of headache in BD patients are attributable to neuro-Behçet's; most are due to migraine and tension headache associated with disease flares. The disease course can be relapsing–remitting, primary progressive or secondary progressive. Acute parenchymal disease is treated with high-dose steroids and disease-modifying drugs such as azathioprine, methotrexate or anti-TNF agents. Cerebral venous thrombosis is treated with anti-inflammatory drugs and anti-coagulants. Cyclosporine should be avoided in neuro-Behçet's if possible. Biologic agents are used in severe, resistant cases, but the duration of treatment needed is unknown. There is a need for evidence-based treatments, and a Neuro-Behçet's Study Group has been established.

A group from Japan presented follow-up data on the treatment of chronic progressive neuro-Behçet's disease with infliximab.[1] They showed that 14 weeks of infliximab treatment could prevent neurological progression in patients resistant to methotrexate by reducing levels of interleukin-6 in the cerebrospinal fluid. They then followed five infliximab-treated patients for up to 2 years; all of these patients were smokers. In the three patients who were able to stop smoking IL-6 levels were low (<20 pg/ml), with or without further infliximab treatment, while levels remained high in the two who continued to smoke irrespective of treatment. It appears that smoking is a cause of resistance to treatment in chronic progressive neuro-Behçet's.

### **Eye disease**

Professor Shigeaki Ohno presented data on the trends in ocular lesions associated with Behçet's disease in Japan.[2] The number of new cases of BD has been decreasing in recent years, and the visual prognosis of patients with eye disease has improved since the introduction of infliximab. Whereas BD used to be the most common cause of uveitis and intraocular inflammation in Japan, it is now in third place behind

sarcoidosis and Vogt-Koyanagi-Harada disease. Of 113 patients with ocular manifestations of BD treated with infliximab, 75% showed marked improvement after 6 months; average visual acuity increased and the average number of ocular attacks had fallen from 3.74 to 0.75. In addition, use of cyclosporine and steroids was reduced and there were only two serious adverse events.

Turkish researchers also looked retrospectively at patients treated with infliximab for eye disease.[3] Ten patients used infliximab for a median of 14 months and, although their mean visual acuity remained stable, the number of ocular attacks per month decreased significantly. For relapse of sight-threatening panuveitis, a Greek study found that a single infusion of infliximab acted faster to reduce inflammation than either intravitreal trimethoprim or high-dose intravenous methylprednisolone.[4] Interestingly, Iranian researchers found that BD patients, especially males, with ocular involvement had higher serum levels of TNF-alpha than did patients without ocular involvement, suggesting a role for TNF-alpha in disease expression.[5]

A German group retrospectively analysed data on 45 patients with ocular involvement in Behçet's disease treated with interferon-alpha for a mean of 34 months and 32 patients treated with cyclosporine A for a mean of 48 months.[6] Fewer recurrences occurred in the interferon-treated patients, and their final visual acuity was better than that of the cyclosporine-treated patients. Four patients were able to discontinue cyclosporine treatment compared with 12 for interferon. An Iranian pilot study of rituximab in 10 patients with longstanding ocular disease resistant to cytotoxic drugs and steroids showed a significant improvement in the Total Adjusted Disease Activity Index, with significant improvement in oedema of the retina, disc and macula after 6 months.[7] Visual acuity and retinal vasculitis also improved, but the results were not statistically significant.

Given the high cost of drugs such as rituximab and infliximab and the need for aggressive treatment to prevent blindness in patients with ocular lesions, researchers in Iran also looked at combinations of cytotoxic drugs.[8] They found that combination therapy of pulse cyclophosphamide, azathioprine and prednisolone was effective in improving visual acuity, posterior uveitis and retinal vasculitis in the long term (up to 5 years).

### **Oral, genital and skin manifestations**

A study carried out in four Greek hospitals looked at the spectrum of mucocutaneous manifestations of Behçet's disease in 202 patients between 1991 and 2007.[9] Around 64% of patients initially presented with oral aphthous ulcers. During follow-up, 65% of male patients and 51% of females had genital ulcers, while more females than males had erythema nodosum (78% versus 43%). Genital ulcers seemed to be more common in these Greek patients than in Lebanese, Turkish and Korean patients, but similar in frequency to German patients. For the evaluation of oral ulcers in BD patients, a Turkish group has developed a composite index that takes into account

patient-derived factors such as pain and functional disability as well as the number and duration of ulcers.[10]

There were several reports of different treatments for oral ulceration. A prospective study in Egypt used twice-daily sublingual tablets of interferon-alpha as a preventive therapy in 21 BD patients, 16 of whom had major aphthous ulcers.[11] After a median follow-up period of 13.5 months, the frequency of ulcers decreased significantly from an episode every 28 days before interferon to once every 61 days after addition of interferon; the duration of aphthosis fell significantly from 9.5 days to 4.6 days. They reported that the cost of this treatment is not very high. A Korean group found that topical tacrolimus applied twice daily for 2 months was effective in reducing the frequency and number of oral ulcers, as well as pain scores, in 15 patients with treatment-resistant recurrent ulcers.[12]

A promising alternative option was presented by Portuguese researchers.[13] In a preliminary study, they told 17 patients with active oral ulcers to take a probiotic yogurt containing *Bifidobacterium lactis* twice a day and assessed their ulcers 3 weeks later. Both the number and duration of attacks were decreased in 10 patients and increased in six, while the frequency of attacks was decreased in nine and increased in eight. *Lactobacilli* seem to have immunomodulatory effects and decrease secretion of pro-inflammatory cytokines; however, larger studies and longer treatment periods are needed to determine the true potential of this therapy. Other promising topical therapies reported by a group in Iraq were zinc sulphate mouthwash and nigella sativa oil.[14][15]

### **Thrombotic complications**

Professor Francisco España from Spain spoke about the endothelium and thrombophilia in Behçet's disease. Endothelial dysfunction associated with vasculitis can lead to thrombophilia. Thrombophilic factors that have been shown to be associated with thrombotic complications of BD include factor V Leiden mutation and the prothrombin G20210A mutation. Inflammation and coagulation are closely related, with a vicious circle whereby prothrombotic factors increase coagulation, which leads to increased pro-inflammatory factors and thus increased inflammation. The protein C pathway is important in the process, and activated protein C is reduced in patients with thrombosis. Defective fibrinolysis is also associated with thrombosis in BD. The fibrinolytic inhibitors thrombin activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor-1 (PAI-1) are increased in patients with BD, but only TAFI is higher in patients with thrombotic complications than in those without. Screening for these various factors could help to assess the individual risk of thrombotic events in patients with BD.

An Italian group reported results of research on endothelial progenitor cells (EPCs).[16] These cells seem to be involved in maintaining vascular integrity and are altered in conditions such as diabetes and atherosclerosis. Circulating EPCs were

found to be greatly reduced in BD patients compared with controls, suggesting that impaired endothelial repair contributes to vascular damage in BD.

A “controversial discussion” was held on the subject of anticoagulation after thrombosis in Behçet’s disease. It was noted that there are no guidelines for screening for vascular involvement in BD. The primary pathology of venous thrombosis in BD is inflammation of the vessel wall, so the main priority is to ensure that immunosuppression is adequate. Additional anticoagulation may help to prevent progression and recurrence of thrombosis in some patients. The recurrence rate is highest in male patients, especially those with the factor V Leiden or prothrombin G20210A mutation. However, the additional benefit of anticoagulation is probably small and is not supported by strong evidence.

### **Paediatric manifestations**

Professor Isabelle Koné-Paut from France gave a lecture on Behçet’s disease at the paediatric age. She defined paediatric BD as disease that meets the criteria for BD before the age of 16 years; it resembles the adult disease but has a stronger genetic component. In juvenile BD, the first symptoms appear before the age of 16 but the criteria are not met until later. The symptoms of BD in children can overlap with those of other rare diseases or of more common inflammatory diseases. In one international survey, onset of PBD occurred between the ages of 1 and 15 years, with 9–12 being the most common age of onset; both sexes were affected in equal numbers, but boys generally had a more severe course. The causes may be infections, toxins or genetic factors, but genetics are very important in the cases with very early onset. Most cases of familial BD have childhood onset.

Treatment recommendations are generally the same as for adult BD, but most of the drugs used are not licensed in children. Colchicine is generally well tolerated and can prevent relapses of uveitis. Corticosteroids are highly toxic in children, so the minimum effective dose should be used and growth hormone may be needed to prevent growth retardation. Azathioprine is effective and well tolerated and can be steroid-sparing. There are some case reports of low-dose thalidomide being effective in treating mucocutaneous lesions. There is little experience of using interferon in children; some case reports in uveitis exist, showing a steroid-sparing effect and ability to stop treatment, although long-term relapse is a possibility. Anti-TNF agents are used to treat juvenile arthritis and Crohn’s disease, but experience in PBD is limited so far.

The PED-BD cohort study is a prospective study supported by the French Ministry of Health to define the natural history of PBD. Charts are reviewed annually to follow symptoms and treatment, and samples are collected to analyse DNA and biological data such as C-reactive protein. About 50 children have been included so far, and the organisers are keen for more people to become involved.

Research in Morocco found that neurological involvement was common in children with BD (16%) and carried a poor prognosis, especially if there is parenchymal CNS involvement.[17] A Turkish study found that around 3% of cases of neuro- Behçet's had paediatric onset.[18] German researchers reported successful treatment with interferon-alpha in two boys aged 14 and 15 with severe treatment-resistant BD with CNS involvement; one patient had complete remission and the other showed marked improvement.[19]

### **Pathophysiology and basic science**

A group of researchers in London investigated the healing of oral ulcers in Behçet's patients.[20] They found that during periods of active ulceration, BD patients fail to increase secretion of epidermal growth factor (EGF) and transforming growth factor-alpha (TGF- $\alpha$ ). These factors produced by the buccal mucosa are important in wound healing. In addition, levels of EGF receptor are high during remission and low during active ulceration, possibly as a result of infection, thus compromising the healing process. Also in the mouth, a Turkish group found increased levels of the salivary peptide HNP 1-3 in BD patients, especially in more severe disease; this peptide has antimicrobial properties.[21]

Korean researchers looked at the cytokine profile in cutaneous lesions of BD.[22] Expression of IL-6 and TGF- $\beta$  was increased in BD skin lesions. However, expression of IL-17 was not increased in the BD lesions despite being high in serum from BD patients and in skin lesions of patients with psoriasis. This work casts some light on the localised pathogenic mechanisms in BD skin lesions.

Researchers based in the Netherlands and the UK, noting the clinical and cytokine profile similarities between BD and Crohn's disease, investigated three specific NOD2 (CARD15) polymorphisms known to be associated with CD.[23] None of the three variant alleles was found in patients with BD. In fact, two of the three alleles were less common in BD patients than in controls, suggesting a possible protective role for these variants.[24] Meanwhile, a Turkish group reported polymorphisms of an IL-18 promoter gene associated with BD.[25]

Work in the UK added weight to the argument that BD is autoinflammatory rather than an autoimmune disease by showing that two genes regarded as masterswitches for autoimmunity are not associated with BD; indeed, one of the genes seemed to be protective.[26] This argument is also supported by the efficacy of interferon-alpha in BD, which could otherwise be seen as paradoxical given the immunostimulatory effects of interferon.[27] Interferon-alpha is known to induce autoimmune diseases such as systemic lupus erythematosus, psoriasis and thyroiditis, but a response rate of 80–90% has been reported in BD.

## **Disease assessment**

The Behçet's Syndrome Activity Score (BSAS) is a patient-completed assessment tool designed for use in research and clinical practice. It takes about 2.5 minutes to complete and consists of 10 questions relating to oral and genital ulcers, skin lesions and current disease activity. A US study in 67 patients showed that the BSAS correlated well with the assessor-completed Behçet's Disease Current Activity Form (BDCAF).[28] Further external validation in other settings is needed.

Patients with BD have a high incidence of chronic streptococcal infections before diagnosis, and a Korean group found that those patients with a high titre of anti-streptolysin O were more likely to have a history of tonsillitis and less likely to have genital ulcers than other patients.[29] They suggested that in these patients, ASO titres could be used to assess disease activity and antibiotics might be effective in treating BD symptoms. Tunisian researchers found that serum levels of B-cell activating factor (BAFF) were higher in patients with active BD than in those in remission, suggesting that this might be a marker for disease activity.[30] In patients with active disease, a positive correlation was found between BAFF levels and skin lesions.

## **New international criteria**

Professor Ahmet Gul from Istanbul introduced the session on the new International Criteria for Behçet's Disease (ICBD). It is important to diagnose BD as early as possible in order to start treatment to prevent long-term damage and improve quality of life. However, developing criteria for diagnosis and classification is difficult because of the multi-system nature of the disease, geographical variations and the existence of different subsets of patients. New biological markers are becoming available but are hard to include in criteria. For diagnostic purposes, criteria need to include as many BD patients as possible, but this may result in the inclusion of patients who do not have BD.

Fereydoun Davatchi from Tehran presented the new ICBD criteria. Between 1946 and 2003, 15 sets of BD criteria were developed; the best known of these are the ISG criteria published in 1990. Validation studies have shown these to have a good specificity but a poor sensitivity and accuracy, leading to the decision in 2006 to develop new criteria for diagnosis of BD. In the new criteria, two points each are given for genital aphthosis and eye lesions, with one point each for oral aphthosis, skin lesions, vascular lesions and positive pathergy test; three points or more indicates BD. In validation studies in various settings, the new criteria have been shown to have a sensitivity of 96.1%, a specificity of 88.7% and an accuracy of 93.8%. They have been presented at several conferences and published in a textbook. Publication in a peer-reviewed journal will follow, as well as further papers defining the individual components.

## **EULAR recommendations**

There were two presentations on the new EULAR recommendations for the management of Behçet's disease (published in the *Annals of Rheumatic Diseases* in January 2008). One presentation covered the literature review on which the recommendations are based,[31] while the other described the nine recommendations.[32] Of 137 articles that met the inclusion criteria, only 20 were randomised controlled trials. Of the nine recommendations, only three (those for eye involvement, joint involvement and mucocutaneous involvement) are based on category I evidence (randomised controlled trials). Robust data on the management of vascular, gastrointestinal and neurological involvement were lacking. The recommendations need to be validated in different countries and settings and will be extended and updated as new evidence becomes available. In the discussion, delegates expressed concern that the recommendations had been produced by EULAR rather than the ISBD and that the experts involved in their development were limited in number and were predominantly rheumatologists.

## **Looking to the future**

In his lecture on new perspectives in Behçet's disease, Professor Hasan Yazici from Turkey made a plea for more hypothesis-based inquiry into BD, more external validation of disease clusters and more basic scientific work on venous endothelium. He proposed that researchers should be looking for ways in which BD differs from the well defined autoinflammatory disorders and that the criteria used for classification and diagnosis should be tailored to subspecialty and ethnic/geographical background and should be dynamic in time.

Closing the conference, Colin Barnes expressed some disappointment that no randomised controlled trials of treatments for BD had been presented and no objective outcome measures had been used. He hoped that by the next conference, there would be fewer descriptive studies of the incidence and manifestations of BD, with a move towards well designed treatment studies and close co-operation between clinicians and scientists.

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