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Behçet's disease (Adamantiades syndrome)

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Behçet's syndrome (BS; Adamantiades syndrome) is the association of the triple symptom complex of recurrent aphthous stomatitis (RAS) with genital ulceration, and eye disease (especially iridocyclitis) though a number of other systemic manifestations may also be seen. BS mainly affects young adult males, and there is an association with HLA-B5 and HLA-B51 (B5101). Features such as arthralgia and leucocytoclastic vasculitis suggest an immune-complex mediated basis, which is supported by finding circulating immune complexes and, although the antigen responsible is unidentified, heat shock proteins have been implicated. An inflammatory disorder, BS is now considered as a systemic vasculitis, characterised by a very wide spectrum of clinical features and by unpredictable exacerbations and remissions.
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Introduction

Behçet's disease, or Behçet's syndrome (BS) is a clinical triad of oral and genital ulceration, and uveitis, tending particularly to affect people with ancestors who lived along the 'Silk Road' particularly Turkey and Japan. Behçet's disease mainly affects young adult males, and there is an association with HLA-B5 and HLA-B51 (B5101).

This condition was first recognised by Hippocrates in the fifth century BC. The condition was later described by the Greek ophthalmologist Benedict Adamantiades (1931), and subsequently, by Hulusi Behçet. As a result some authors prefer the term 'Adamantiades–Behçet Syndrome'. However, it was Behçet who described the classical clinical triad of oral and genital ulceration with ocular inflammation.

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Epidemiology

Behçet's syndrome occurs throughout the world with varying prevalence but is rare, with an occurrence of one case per 100 000 in the developed world and a frequency tenfold higher in the Middle East. It is most common in the Mediterranean Countries, South East Asia (2–20/100 000), in the so-called 'silk route' countries (13–370/100 000) and particularly in countries such as Japan (13–30/100 000) and Turkey (80–370/100 000). It is uncommon in Western Europe and the USA (from 0.1 to 7.5 patients per 100 000 inhabitants). There is also an increased prevalence in certain ethnic groups, while the prevalence of the disease is also dependent on the geographic area of their residence.

Both genders are equally affected, although large series of patients in certain Mediterranean countries and the Middle East showed that there is a male predominance (1.5–5:1). Male gender is also a risk factor for severe disease (Dilsen, 2000). Familial occurrence has been reported in 1–18% of patients, mostly of Turkish, Israeli and Korean origin.

The disease onset can be at any age, but is typically in the third decade. Few neonatal cases have been reported, and children are rarely affected. Early onset is associated with more severe disease.

Aetiopathogenesis

Behçet's syndrome is found worldwide, but it is most common in the Eastern Mediterranean countries and in eastern Asia, China, Korea and Japan. This distribution of disease may represent, not the passage of traders, but the earlier demographic movements across Asia and the Beringia Landmass some 10 000–30 000 years ago. In those countries, BS is a leading cause of blindness though this is not the case in the Western world.

There is an association with HLA-B5 and especially HLA-B51 or its B101 allele in Japan, Korea, Turkey and France, as well as with the presence and severity of ocular manifestations in Britain (Verity *et al*, 1999a). The B5108 allele has also been shown to be associated with BS (Mizuki *et al*, 2001). However, HLA-B52,

which differs from HLA-B51 by only two amino acids in the peptide-binding groove, is not associated with BS in any population tested. This suggests that selective peptide binding may influence disease risk. However, it is still unclear which specific peptides are bound to HLA-B51 (Verity *et al*, 2003c).

Nevertheless, HLA-B51 cannot be the sole causative factor as roughly one third of patients with BS, even in high-risk countries, do not possess the gene. Further, the odds ratio (OR) of BS in an individual positive for HLA-B51 shows a wide variation across both Europe and Asia (Verity *et al*, 1999b). A possible explanation for this may lie in the fact that the HLA-B51 molecule expresses the Bw4 motif which itself may be causally related to BS, being found in other HLA types variably related to the disease (HLA-B15, HLA-B27 and HLA-B57) (Verity *et al*, 2003b).

Behçet's syndrome has a second association – with the MHC class 1 chain related (MIC) family of genes, which are situated between the tumour necrosis factor (TNF) and HLA B genes. The prevalence of a 'triplet repeat' polymorphism in the transmembrane region of the MICA gene (MICA A6 allele – thought to be in linkage disequilibrium with HLA-B51) is raised in Japanese and Middle Eastern patients with BS (Mizuki *et al*, 1997). In addition, a second MICA gene, encoding part of the extracellular region of the molecule (MIC 009 allele) has been found to be raised in BS (Wallace *et al*, 1999).

Further associations have been shown between BS and genes coding for TNF and heat shock proteins (HSP), which are discussed further below. Allelic variants of these genes are also in linkage disequilibrium. An association with the alleles in the TNF promoter region was first reported in Japanese patients with BS (Mizuki *et al*, 1997) and later confirmed among Middle Eastern patients (Verity *et al*, 1999a). It is proposed that two alleles at this site may be in linkage with HLA-B51 and may be co-inherited, so contributing to both the disease risk and to the severity of the disease.

Recently a novel susceptibility locus for BS has been mapped to chromosome 6p22-23 (Gul *et al*, 2001).

Behçet's syndrome has not been proved to be infectious, contagious, or sexually transmitted. The immunological changes seen in Behçet's disease mimic those seen in patients with recurrent aphthous stomatitis (RAS) (Freysdottir *et al*, 1999), with various T-lymphocyte abnormalities (especially T-suppressor cell dysfunction), changes in serum complement, and increased polymorphonuclear leucocyte motility. There is also evidence that mononuclear cells may initiate antibody dependent cellular cytotoxicity to oral epithelial cells.

Features such as arthralgia and leucocytoclastic vasculitis suggest an immune-complex mediated basis, which is supported by finding circulating immune complexes, and heat shock proteins (HSP) have been implicated (Hasan *et al*, 1996; Freysdottir *et al*, 1999) but there is some evidence for a viral (possibly herpes simplex) aetiology. Herpes simplex virus and hepatitis viruses have been proposed as causal agents of BS (Ilter *et al*, 2000) but no causative correlation established (Cantini *et al*, 1997). Similarly a number of bacteria have been implicated including *E. coli, Klebsiella pneumoniae* and *Mycoplasma fermentas* (Zouboulis *et al*, 2003). Several streptococci including *Streptococcus sanguis* have been implicated (Lehner, 1997; Direskeneli *et al*, 2000) but the antigen responsible has not been identified.

The multiplicity of aetiologic factors may have a common denominator in the HSP particularly 65 kDa microbial HSP, which shows significant homology with the human 60 kDa mitochondrial HSP. Indeed, the uncommon serotypes of *S. sanguis* found in BS cross-react with the 65 kDa HSP, which also shares antigenicity with an oral mucosal antigen. T-cell epitope mapping has identified four peptides derived from the sequence of the 65 kDa HSP that stimulate specifically TCR+ lymphocytes from patients with BS. These peptides (111–125, 154–172, 219–233 and 311–325) show significant homology with the corresponding peptides (136–150, 179–197, 244–258 and 336–351) derived from the human 60 kDa HSP. B-cell epitopes within mycobacterial HSP 65 or human HSP 60 overlap with the T-cell epitopes and both IgG and IgA antibodies have been identified. Among the four T- and B-cell epitopes, peptide 336–351 of the 60 kDa HSP is significantly associated with BS in UK, Japan and Turkey. HSP 60/65 was also found to be significantly increased, in the epidermal cells of skin lesions in BS, and antibodies to HSP 65 were significantly raised in the cerebrospinal fluid from patients with neurological manifestations of BS (Pervin *et al*, 1993).

There is also a decreased T-helper (CD4): T-suppressor (CD8) ratio and evidence of disturbance of NK cell activity and increased pro-inflammatory cytokines. The TH-1 cytokine interferon (IFN-γ) is raised in serum, in T cells of skin and CSF and interleukin-12 (IL-12) is generated by stimulation of CD4+ T cells with the HSP peptide 336–351, though IL-12 can also be secreted by neutrophils in BS. However, the concentration of the TH-2 cytokine IL-6 also is increased in the serum, especially in the active stage, as was also found with IL-10 on stimulation of peripheral blood mononuclear cell. Stimulation with *S. sanguis* (KTH-1) of T-cell lines generated from patients with BS suggests that TH-1 type mRNA is induced (IL-2 and IFN-γ). Investigations of intracellular IFN and IL-4 suggest that there is a polarisation toward the TH-1 type of cells in patients with active BS, because of a significant increase in the intracellular IFN-γ that was not observed with IL-4.

Circulating immune complexes and changed levels of complement are found and there is immunoglobulin and complement deposition within and around blood vessel walls and raised levels of acute phase proteins. Circulating autoantibodies against a number of components, including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm are present. Vasculitis, usually leucocytoclastic vasculitis is the common denominator. Immunocytes, (mostly CD4 cells), B cells, and neutrophils are infiltrated perivascularly. Prostanoid synthesis in endothelial cells or vessel walls is impaired, whereas von Willebrand factor,

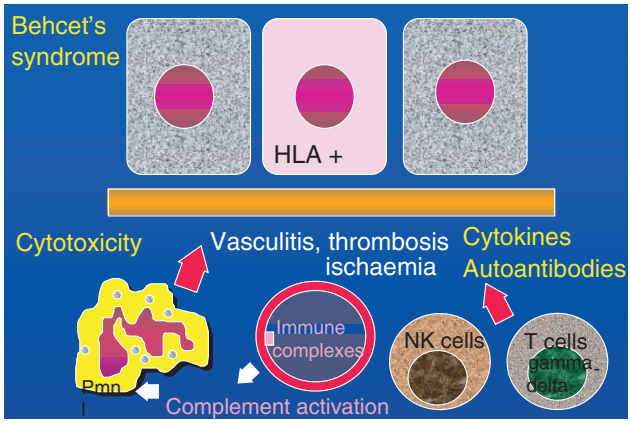

Figure 1 Pathogenesis of BS

endothelin (ET)-1,2, thromboxane and thrombomodulin are increased and hypercoagulability is a feature. The possible pathogenesis is summarised in Figure 1.

Clinical features

Behçet's syndrome is a chronic multisystem and sometimes life-threatening disorder (Table 1). The clinical picture may take some time to develop but is usually complete in a mean of 15 months from the time of onset. Very non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulcerations by 6 months to 5 years. These include:

- malaise,
- anorexia,
- weight loss,
- generalised weakness,
- headache,
- perspiration,
- decreased or elevated temperature,
- lymphadenopathy,
- pain of the substernal and temporal regions.

A history of (1) repeated sore throats, (2) tonsillitis, (3) myalgias and (4) migratory erythralgias without overt arthritis.

Behçet's syndrome is characterised mainly by the following.

- *Recurrent aphthous stomatitis* (RAS): in 90–100% of cases. Recurrent aphthous stomatitis is the most common and usually the initial manifestation of BS (Figure 2). However, only a few patients with RAS progress to BS and it is not possible to determine which, or when the transition may occur. Recent HLA and immunological findings may eventually help in this respect. Erythema may also be seen on the mucous membranes.
- *Recurrent painful genital ulcers* that tend to heal with scars in 64–88% of cases. Genital ulcers are especially common and larger in females with BS, and resemble RAS (Figure 3). In males they are often on the scrotum and penis (Figure 4) and in both genders may be localised around the anus.
- *Ocular lesions*: inflammatory eye disease occurs in about 70% of all patients (Verity *et al*, 2003c) and typically occurs after the onset of oral ulceration. Intra-ocular inflammation is the presenting feature in over 10% of cases and rarely may not be associated with oral ulceration. The most common ocular manifestation is relapsing iridocyclitis. Uveitis, uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), and optic atrophy occur. Interestingly, conjunctival ulceration is rare (Matsuo *et al*, 2002; Verity *et al*, 2003a). Both eyes are usually eventually involved, although uniocular disease occurs in 6%, and blindness may result.
- *CNS lesions*: are predominantly parenchymal and are due to a small vein inflammatory process and present with disseminated or focal CNS dysfunction. They are

Table 1 Behçet's disease: clinical features and possible complications

Oral
Aphthous stomatitis
Ocular
Uveitis and hypopyon
Retinal vasculitis
Optic atrophy
Blindness
Genital
Ulcers
Cutaneous
Pustules
Erythema nodosum
Joints
Arthralgia (large joints)
Vascular
Aneurysms
Thromboses of vena cava
Renal
Proteinuria
Haematuria
Neuropsychiatric
Syndromes resembling multiple sclerosis
Syndromes resembling pseudobulbar palsy
Benign intracranial hypertension
Brainstem lesions
Depression

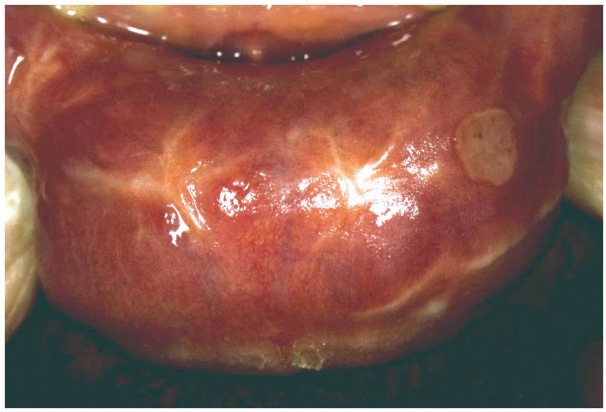

Figure 2 Oral ulceration with evidence of scarring from previous episodes

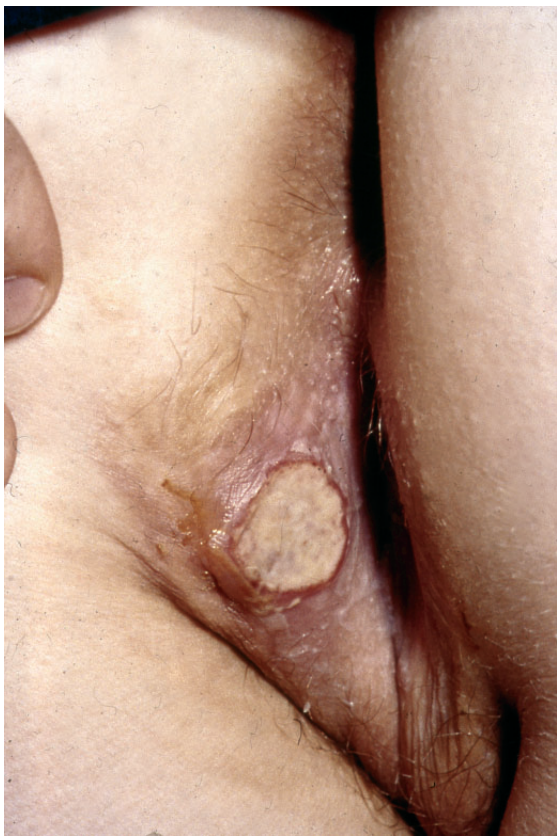

Figure 3 Labial ulceration

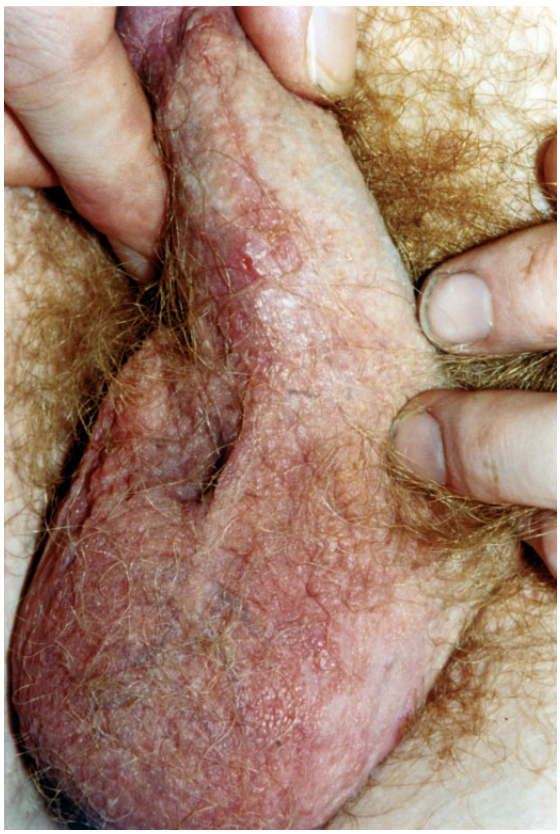

Figure 4 Penile ulceration

usually sub-tentorial (cerebellum, brain stem and spinal cord), and include meningoencephalitis, cerebral infarction, psychosis, cranial nerve palsies, cerebellar and spinal cord lesions, hemi- and quadriparesis. The non-parenchymal form involves large veins and leads to dural sinus thrombosis and cranial hypertension. Clinical course, management and prognosis of these two major forms are different (Siva, 2001).

- *Skin lesions*: occur in approximately 60% of cases and may take the form of erythema nodosum, pustular lesions and papulopustular lesions (Figures 5 and 6) and acneiform nodules. Venepuncture is, in some patients, followed by pustulation but this phenomenon (*pathergy*) (Figure 7), said to be characteristic of BS is not seen often in UK patients.
- The joints, epididymis, heart, intestinal tract, vascular system and most other systems may also be involved. Large vein thrombosis (of inferior vena cava and cranial venous sinuses) can be life threatening.

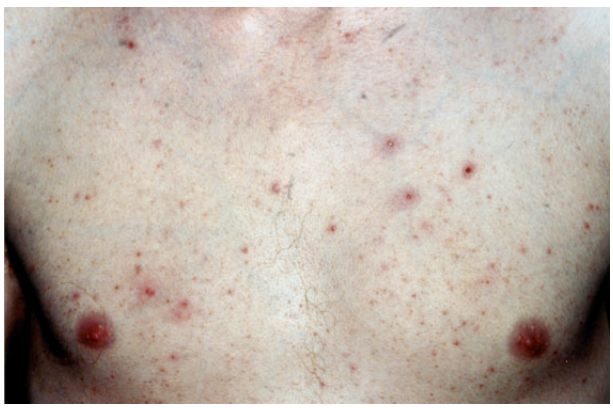

Figure 5 Cutaneous papulopustular rashes – chest

Complications

Behçet's syndrome runs a chronic course with unpredictable exacerbations and remissions but although the frequency and severity of attacks may reduce over time, there is no way of prognosticating. Chronic morbidity is usual; the leading cause being ophthalmic involvement, which can result in blindness. The effects of the disease may be cumulative, especially with neurologic, vascular, and ocular involvement. Mortality is low but can occur from neurologic involvement, bowel perforation, extensive thrombotic events, or rupture of arterial aneurysms, or as a complication of immunosuppressive therapy. Male patients with an early age of onset appear to have a worse prognosis while a severe deterioration is seen in 20% of patients. In the face of the serious potential complications, patients with suspected BS should be referred early for specialist advice.

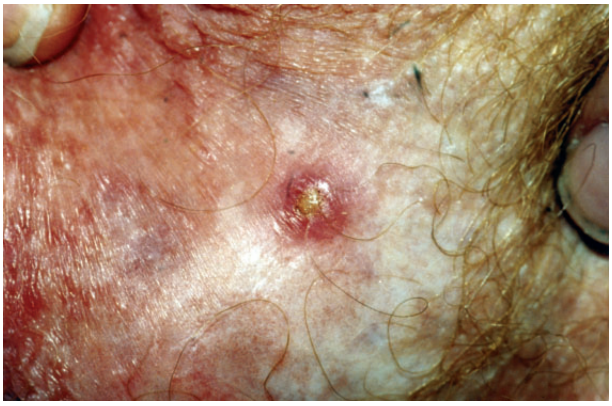

Figure 6 Scrotal papulopustular eruption with evidence of scarring

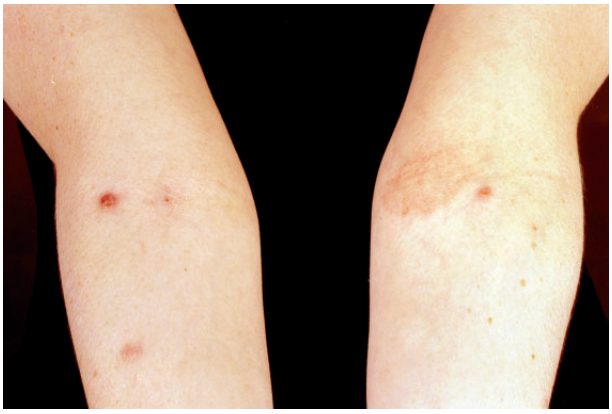

Figure 7 Pathergy following venesection

Diagnosis

Because BS is rare, the prodrome so non-specific and the symptoms of established disease overlap those of other diseases, it can be very difficult to diagnose.

A clinical diagnosis of BS is usually made on the presence of any two of oral, genital and ocular features, but similar oral ulceration may also develop in other diseases which have multi-system involvement and which must be excluded when making the diagnosis. The BS must enter into the differential diagnosis of RAS but the diagnosis may be difficult to confirm for reasons given earlier. Oral and genital ulceration may also result from folate deficiency, when other features characteristic of BS are lacking. Recurrent oral, ocular and genital lesions may also be seen in erythema multiforme and sometimes in ulcerative colitis and other conditions.

According to the *International Criteria for Classification of Behçet's Disease*, the primary features are:

- recurrent oral ulceration (painful aphthous ulcers, testing negative for herpes) in almost 100% of patients;
- plus any two of the following four:

1. recurrent genital ulcerations (resembling oral ulcers, usually painful, testing negative for herpes);
2. eye inflammation (uveitis, cells in the vitreous or retinal vasculitis);
3. skin lesions (erythema nodosum, pseudo-folliculitis, papulopustular lesions or acneiform nodules consistent with Behçet's disease, observed by a physician in postadolescent patients not receiving corticosteroids);
4. a positive pathergy test performed during active BS symptoms. The pathergy test is performed by piercing a sterile 20-gauge needle subcutaneously into the forearm, without injection of saline. It is considered as positive when the puncture leaves an aseptic erythematous nodule or pustule larger than 2 mm. in diameter after 24 or 48 h. However, UK or US patients rarely test positive, even during disease activity. Indeed only 20–60% of Behçet's patients present positive pathergy tests.

Other manifestations that may be useful in diagnosis, but are not considered part of the International Behçet's Criteria include:

- subcutaneous thrombophlebitis, deep vein thrombosis;
- epididymitis, arterial occlusion and/or aneurysm;
- central nervous system involvement (including difficulties in movement or speech or memory loss);
- severe headaches with stiff neck, joint pain or non-destructive arthritis;
- GI tract involvement (bloating, cramping, diarrhoea and bloody stools);
- renal involvement;
- pulmonary vascular inflammation and pleuritis.

Reliable diagnostic tests for BS are not available but there are many immunological findings including circulating autoantibodies against components including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm; circulating immune complexes and abnormal levels of complement; immunoglobulins and complement deposition within and around blood vessel walls and a depressed T-helper (CD4): T-suppressor (CD8) ratio.

Behçet's disease is thus diagnosed mainly on clinical grounds alone though findings of HLA-B5101 and pathergy are supportive, as are antibodies to cardiolipin and neutrophil cytoplasm. Activity of the disease may be assessed by serum levels of acute phase proteins or antibodies to intermediate filaments, both of which are raised in active BS.

Medical and ophthalmological opinions should be obtained since ocular involvement often culminates in impaired sight.

Differential diagnosis

This is from other oculomucocutaneous syndromes.

- Sweet's syndrome: oral ulcers, conjunctivitis, episcleritis, inflamed tender skin papules or nodules.
- Erythema multiforme: erosions and target (iris) lesions.
- Pemphigoid: bullae and erosions.
- Pemphigus: erosions and flaccid skin bullae.
- Reiter's syndrome: ulcers, conjunctivitis and keratoderma blenorrhagica.

- Ulcerative colitis.
- Herpes simplex.
- Syphilis.
- Lupus erythematosus.
- Mixed connective tissue disease.

Management

A variety of treatments have been tried for those with multi-system lesions of BS, but results have in many cases been inconclusive, especially as the disease is subject to spontaneous transient remissions.

Systemic immunomodulation

Corticosteroids
Available treatments include systemic corticosteroids, which are indicated for the treatment of active BS, although there have been no randomised double blind placebo controlled trials (RCT).

Azathioprine
Azathioprine is often beneficial and may act as a disease modifying drug, particularly in those with recent onset eye disease (Hamuryudan *et al*, 1997). In an RCT using 2.5 mg kg^{-1} body weight per day for 2 years it was shown to reduce the onset of new eye disease and there were fewer episodes of hypopyon uveitis in those patients with established eye disease (Yazici *et al*, 1990).

Colchicine
Colchicine is often of benefit and has also been shown to be beneficial for genital ulcers erythema nodosum and arthritis (Yurdakul *et al*, 2001).

Thalidomide
In certain circumstances thalidomide may be the most effective treatment for otherwise intractable oral ulceration. An RCT showed significant improvement in oro-genital ulcers and follicular lesions at both 100 and 300 mg day^{-1} (Hamuryudan *et al*, 1998). However, polyneuropathy was noted in both cases and there was an increase in the frequency of episodes of erythema nodosum. Recently the risk of polyneuropathy has been shown to be minimal at doses below 25 mg day^{-1} (Bastuji-Garin *et al*, 2002).

Ciclosporin and tacrolimus
Ciclosporin has been shown to be effective in small open studies while tacrolimus has been beneficial in a small series of cases of posterior uveitis refractory to ciclosporin (Sloper *et al*, 1999).

Others
Interferon α-2a has recently been subjected to a RCT and showed decreased pain and duration of oral ulcers, frequency of genital ulcers and papulopustular lesions (Alpsoy *et al*, 2002).

Other medications which have been used, but for which there is no RCT include levamisole, cyclophosphamide, dapsone, methotrexate, mycophenolate mofetil, pentoxifylline and chlorambucil. Most recently there has been interest in the use of chimeric anti-TNF alpha monoclonal antibody (Infliximab). Several case reports and small open studies have shown Infliximab to benefit in the management of ocular, cutaneous and oro-genital lesions (Stokes and Kremer, 2003), but the results of a formal RCT are awaited.

Oral lesions
Oral lesions may be managed symptomatically like RAS. Topical corticosteroids are the drugs of choice.

Websites and patient information

The American Behçet's Association
http://www.w2.com/Behçets.html
http://www.aarda.org/indexf.html
http://www.emedicine.com/derm/topic49.htm

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