Update on Behçet's Disease

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Abstract: Behçet’s disease was initially described a triad of symptoms including oral aphthous ulcers, genital ulcers and uveitis. It was subsequently found to be a multisystem disease characterized by other manifestations involving the articular, cutaneous, neurological, vascular, gastrointestinal and pulmonary systems. Over past years, new information has added to our understanding of this disease. This article summarizes an update in the classification criteria, pathophysiology, clinical manifestation and treatment options in Behçet’s disease.

Keywords: Behçet’s disease, Pathophysiology, Treatment

Introduction

Behçet’s disease (BD) is a chronic inflammatory disease first described by Hulusi Behçet in 1937 as a triad of symptoms, namely oral aphthous ulcers, genital ulcers and uveitis. The disease is indeed recognized worldwide and its severity tends to correlate with its prevalence. Over the past years, there have been ongoing studies and research to help add to the understanding of this disease. Improved recognition and reporting has contributed to physicians’ awareness on some of the latest developments. This review highlights the recent update in the classification criteria, pathophysiology, neuro-manifestation as well as latest treatment options in Behçet's disease.

Epidemiology

BD is also known as the “Silk road disease” because it is most commonly seen in the region along the ancient trading route extending from the Mediterranean to the Far East. Its prevalence differs in different ethnic groups. It ranges from less than 1 per 100,000 in United Kingdom to around 400 per 100,000 in some part of Turkey. Some clinical manifestations show regional difference. The gastrointestinal involvement is more common in the Far East but rare in Turkey. More positive pathergy tests were observed in the Turkish and the Japanese than in the Northern European and Americans. BD is rare in Hong Kong. According to Mok et al, only 37 adult patients were classified as BD from four regional hospitals between the years 1978 to 2000. Local BD runs a more benign course. The presenting features at the time of diagnosis were oral ulceration (100%), genital ulcers (81%), skin lesions (73%), arthritis/arthralgia (54%) and ocular lesion (35%). Other major organ involvement was rare.

Classification Criteria

There are no specific symptoms, signs nor laboratory findings in BD. The diagnosis is made merely by recognizing a group of clinical features. Hence various experts have developed various clinical criteria. More than ten sets of classification criteria have been developed internationally since 1946. The Diagnostic Criteria defined by the 1990 International Study Group (ISG) for BD is one of the more commonly cited ones. In the ISG criteria, recurrent oral ulceration is a pre-requisite, plus any two of the following features include recurrent genital ulceration, eye lesions, skin lesions or positive pathergy test.
However, Fereydoun Davatchi showed that this classification criterion has good specificity, poor sensitivity and accuracy for the diagnosis of BD in the Iranian. This led to the development of a new International Criteria of Behçet’s Disease 2006 (Table 1). Validation studies showed that this new criterion has a sensitivity of 96.1%, a specificity of 88.7% and an accuracy of 93.8%.

**Pathophysiology**

**Genetics**

The exact pathophysiology of BD remains unknown. It is generally accepted as an intense inflammatory reaction in a genetically predisposed host. Among all the genes that have been proposed to play a role, human leukocyte antigen-B51 (HLA-B51) has the strongest association. 6,7 The genetic association of HLA-B51 among different ethnic groups nearly corresponds with global disease distribution of BD. Countries with high prevalence of HLA-B51, like Greece, Turkey, Middle East, Iran and Japan, were found to associate with high BD prevalence. While in those ethnic groups with low HLA-B51 prevalence, like the European and the African, BD is similarly infrequent.6 Apart from HLA-B51, the associations with other HLA alleles may have prognostic significance in BD patients. Bettencourt et al found that HLA-B27 allele was increased in the severe Portugal BD patients but absent in those with mild disease.8

Indeed, many other non-HLA genes may also correlate with BD. From whole genome screening of multi-case families, BD was found to have genetic association with at least 16 different non-HLA susceptibility foci. In the Turkish population, tumor necrosis factor-α (TNF-α) allele was found to be linked with disease susceptibility as well.10 Small ubiquitin-like modifier 4 (SUMO4) gene is involved in autoimmune and inflammatory responses through down regulation of NF-κκκκκ signal, leading to decrease transcription of pro-inflammatory cytokines. Its’ polymorphism has been shown to correlate with type I diabetes in several Asian populations. Hou et al found that SUMO4 +438C allele associates with susceptibility to BD in HLA-51 negative Chinese Han patients, while the AGAT haplotype is protective against BD in HLA-B51 negative patients.11 Polymorphism in the natural resistance associated macrophage protein (NRAMP1) gene, also named as solute carrier family 11 member A1 gene (SLC11A1) seems result in different BD susceptibility in different ethnic group. SLC11A1 exerts its’ role by up-regulating TNF-α, inducible nitric oxide syntase (iNOS), and major histocompatibility complex (MHC) class II genes expression. Kim et al concluded SLC11A1 polymorphism may offer a protective effect against BD in the Korean population.12 while the others found another genetic polymorphism in SLC11A1 may be one of the plausible candidate genes of BD in Turkish.13

**Immunopathogenesis**

Apart from underlying genetic predisposition, immune dysfunction plays a crucial role in BD. It has been shown that the pathergy test at 4 hours was mediated by neutrophils and lymphocytes in the absence of vasculitis.14 At 48 hours, the dermis in the pathergy test was infiltrated by mononuclear cells composed mainly of T lymphocytes.15 This suggested the role of T lymphocytes in the disease progression of BD. It is postulated that T cells in BD are hypersensitive to a variety of antigens, and this hypersensitivity triggers off the immune cascade in BD. The activated T cells recruit and activate monocytes through CD40-CD154 interaction and other T cell derived cytokines. The turned-on monocytes produce IL-12, leading to the shift to Th1 response. And in consequence to T cells activation and production of proinflammatory cytokines such as TNF-α, IFN-γ, IL-8 and IL-17, neutrophils were primed and activated.16, 17 A number of antigens induce T cells hypersensitivity. These include antigens from viruses, bacteria; heat shock proteins and some autoantigens. For example, in BD uveitis, autoimmunity to retinal antigens (like the S-antigen, a soluble protein in retina and pineal gland and α-enolase, a glycolytic enzyme present in many tissues) is well known. Antibodies to the selenium binding protein have recently found to associate with Behçet’s uveitis.18

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<td>Oral aphthosis</td>
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<td>Skin lesion</td>
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<td>Vascular lesion</td>
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<td>Positive pathergy test</td>
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<td>Genital aphthosis</td>
<td>2</td>
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<td>Eye lesion</td>
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3 points or more indicates Behçet’s disease
According to a study by Choi et al, antibodies against saccharomyces cerevisiae (ASCA), which is a species of budding yeast used in baking and brewing, are present in 44% of BD patients with active gastrointestinal (GI) involvement, compared to only 3% in those without active GI manifestation.

**Vasculopathy in Behçet's Disease**

Vascular involvement is not uncommon in those high disease prevalence ethnic groups. Venous thrombosis composes majority of cases with vascular presentation. What gives rise to such a 'prothrombotic state' in BD remains uncertain. Studies have been done to try looking into the pathogenic mechanism behind. This prothrombotic phenomenon seems not related to the deficiency of protein C, protein S, antithrombin III and factor V Leiden. Though there is increase in thrombin, thrombomodulin generation as well as fibrinolysis, these were not related to thrombosis observed in BD. In that case, coagulopathy may not explain the thrombosis in BD. Study shown a higher prevalence of anti-endothelial cell antibodies in the sera of BD patients and their presence correlated with the clinical activity. Whether or not the presence of anti-endothelial antibodies predispose to thrombosis remains to be elucidated.

Concerning arterial involvement, it mainly manifests as arterial occlusion and aneurysm formation. Histologically, the inflammation involving the vessel wall is mainly confined to the adventitial layer. And the number of vasa vasorum with infiltration of neutrophils and lymphocytes was significantly increased in vasculo-Behçet's disease compared with that observed in other inflammatory aneurysms. This suggested BD arterial inflammation probably caused by a neutrophilic vasculitis directed at the vasa vasorum, causing arterial wall degeneration and subsequent aneurysm formation.

**Cyclosporin A and Neuro-Behçet's Disease**

Though rare, neurological features occur in 5 to 10% of BD patients. The neurological features contribute significantly to both morbidity and mortality. Among those with neurological manifestation, more than 70% of them affect the brain parenchyma, involve the brainstem, cerebral and/or cerebellar hemispheres or spinal cord. It gives rise to sensorimotor symptoms/signs, long tract signs, cranial nerves palsies and cerebellar dysfunction. The remaining 25% of patients present with non-parenchymal features in the form of dural sinus thrombosis. The manifestations are typical symptoms and signs of increased intracranial pressure.

Three case-control studies have reported more neurological manifestations in BD patients who have received cyclosporin A than in those who did not. In the study by Kötter and colleagues, among 117 studied cases (all were adult, fulfilled the ISG criteria or the Dilsen criteria for the classification of BD, 4 largest treatment groups identified were steroid, interferon, azathioprine and cyclosporine A, frequency of ocular disease in the 4 groups were 61%, 96%, 76% and 71% respectively), 10 developed neurological manifestations and all presented with parenchymal involvement. Six of them were on maintenance cyclosporin A treatment and the other four were untreated at the onset of neurological symptoms. All 6 cases came from 21 cyclosporine A treatments. In contrast, those treated with other regimens had no new neurological manifestations. This difference was significant. Regarding the use of cyclosporine A in BD, the increased risk of neurological complication raises caution amongst doctors. In the latest European League Against Rheumatism (EULAR) recommendations for the management of Behçet's disease, it suggested that cyclosporin A should not be used in patients with BD with central nervous system involvement unless necessary for intraocular inflammation.

**New Treatment Option for Behçet's Disease**

Generally, in patients with mild mucocutaneous and/or arthritic symptoms, local steroid and oral colchicine are the drugs of choice. In case of moderate to severe mucocutaneous lesions, vascular, neurological and GI symptoms, systemic steroid or other immunosuppressants should be considered. Azathioprine plus steroid are the core drug treatments for uveitis. For patients with refractory eye involvement, cyclosporin A is the drug of choice.

Anti-tumor necrosis factor (TNF) agents have recently received considerable attention in BD. Amongst all anti-TNF agents, infliximab is the drug most studied. It was first described as a rapid and effective treatment for 5 patients with relapsing uveitis. After a single infusion at the dosage of 5 mg/kg; it decreased the ocular inflammation by 50% on day 1 and 90% by day 4. By day 7, the retinal infiltrates and vasculitis had completely resolved in all patients. Subsequent three open prospective studies have demonstrated that infliximab was able to reduce the frequency of uveitis relapse.
significantly during treatment period. In addition to reducing frequency of relapse; infliximab improved visual acuity, reduced muco-cutaneous lesions and spared the use of other immunosuppressants. Among the three studies, only one case of tuberculosis was reported.

So far, there have been no controlled trials on the efficacy of treatments for any sort of neurological involvement in BD. For the use of infliximab in neuro-Behçet, only case reports available. Infliximab seems to have a role in patients who failed to response to other immunosuppressive agents.

Naganuma et al looked into the efficacy of infliximab for induction and maintenance of remission for fluminant intestinal BD. Among 6 patients with steroid dependent intestinal BD and were refractory to immunosuppressants, 4 of them achieved remission by infliximab and the remission was maintained with scheduled treatment of infliximab, with the longest remission for about 3 years. The other 2 required surgery and one of them has maintained remission by infliximab for 2 years after operation. It seemed that infliximab is a good choice as induction and maintain remission in severe intestinal BD.

Etanercept was showed to suppress most of the muco-cutaneous lesions when compared to placebo in a double-blinded placebo controlled trial.

For adalimumab, there is limited data to support its' use in BD currently.

Concerning the safety issue with the use of anti-TNF agents in BD, we have to always bear in mind the major side effects include infection, demyelinating disease, malignancies and congestive heart failure. Either short-term or long-term administration of infliximab was well tolerated in almost all BD patients published so far. The reported adverse events were usually mild. 2 cases developed tuberculosis.

In the latest published recommendations for the use of anti-TNF treatment in BD, these biologic agents should be reserved for use in selected cases including those with new onset bilateral posterior uveitis or unilateral uveitis with poor visual acuity, recurrent or refractory uveitis despite immunosuppressants, those with severe neurological, intestinal, mucocutaneous and arthritic involvement that are not controlled by first line treatment and immunosuppressive agents.

B cell depletion therapy has also been reported to be effective in difficult cases of BD. A case of resistant retinal vasculitis, refractory to azathioprine, local and systemic steroid, subsequent methylprednisolone and etanercept, was effectively treated with rituximab infusion. Remission was sustained for up to 24 months.

A randomized, single blind controlled study to evaluate the efficacy of rituximab in treating severe ocular manifestation of Behçet's disease is completed and awaiting to be published.

Other novel treatments reported to reduce the number of oral ulcers include probiotic yogurts containing the bacteria Bifidobacterium lactis, topical tacrolimus, sublingual tablets of interferon-α, zinc sulphate mouth wash and nigellar sativa oil.

In 2008, the European League Against Rheumatism (EULAR) published a comprehensive recommendation for the management of BD. Treatments suggested for ocular, mucocutaneous and arthritic symptoms are mostly evidence-based. However, recommendations for vascular, neurological and intestinal involvement were largely based on expert opinion and uncontrolled evidence due to lack of controlled studies for these rare and potentially fatal manifestations.

### Conclusion

Behçet's disease like other chronic inflammatory disease is a complicated disease entity with various clinical manifestations and severity of symptoms. With new advances and innovative concepts, we are looking forward to further new studies and breakthrough management in this disease.

### References


