Management of the patient with Behçet’s disease

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Introduction

Behçet’s disease (BD) is a multisystem disorder characterized by vasculitis. It was first described in 1937 by Hulusi Behçet and consists of a triad of recurrent ulcers of the oral and genital mucosa with relapsing uveitis. Since the initial description, additional organ involvements have been reported.

The aetiology of BD is not known. Although viruses, streptococcal infection, autoimmune mechanisms, and endothelial-cell dysfunction have been postulated in the aetopathogenesis, no definite cause has been identified so far [1,2]. The disease is most frequently seen in the Middle East region and Japan, suggesting a role for genetic and/or environmental factor(s). An increased prevalence of HLA-B51 (5) antigen has been reported in patients with BD, possibly pointing to genetic factors in the pathogenesis of this disorder [3].

Clinical features

Because of the relatively frequent renal complications of BD, it is useful for the clinical nephrologist to be aware of the main clinical characteristics of this disease and the therapeutic options that are available today. The onset of BD is usually early in the third decade of life and occurs infrequently before puberty and after age of 40. Males are affected more frequently than females and they have a more severe course. Behçet’s disease usually runs an undulating course of exacerbations and remissions that gradually abate by time.

Many organs or systems may be affected in BD. The most frequent initial manifestations are oral and genital ulcerations, but many patients present to a physician with more severe clinical problems, usually affecting the eyes, joints, blood vessels, central nervous system, kidneys, or gastrointestinal system.

The oral ulcers are usually painful, with a central yellowish necrotic base, and they appear singly or in crops. According to the ISG criteria, oral ulcerations must recur at least three times in one 12-month period. Preferential sites of ulceration are the mucous membranes of the lips, gingiva, buccal mucosa, and tongue. The palate, tonsils, and pharynx are rarely involved. The majority of oral ulcerations are minor aphthous ulcers, but fusion of several ulcers may produce a single large ulcer on rare occasions. Most of oral

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aphthous ulcers heal without scarring within 1 or 2 weeks, but large ulcers may leave scars.

The genital ulcers resemble the oral ones, but they are usually deeper and tend to leave scars after healing. Therefore, a careful examination should include the perineal region. Genital ulcers are most frequently located on the scrotum and the vulva. The penis and the perianal and vaginal mucosa may also be involved.

Vascular involvement is the leading cause of death in BD, with an approximate prevalence of 25% [5]. Vascular involvement is more frequent in males than in females (36% vs 14%). Three forms of vascular disease (venous occlusions, arterial aneurysms, and/or arterial occlusions) are found in BD. Venous lesions occur more frequently than arterial lesions (88% vs 12%). Symptoms of vascular disease vary depending on the site of involvement [1,2,5]. Aneurysm and/or occlusion of the arteries of the upper or lower extremities are the most frequent type of arterial lesions. Pulmonary arterial vasculitis presenting with dyspnoea, cough, chest pain, and haemoptysis is not rare. Aneurysms of renal arteries may be responsible for hypertension. Occlusion of the subclavian artery frequently leads to a diminished pulse in the ipsilateral upper extremity. Femoral pain, intermittent claudication, and avascular necrosis of the head of the femur may occur, caused by either aneurysm or occlusion of the femoral artery. Involvement of the common carotid artery may result in development of hemiplegia. Ruptures of large arterial aneurysms may lead to death. Subcutaneous thrombophlebitis is the most frequent (47%) type of involvement of veins [5]. The next most common venous lesions are superior and inferior vena cava occlusions. Chronic obliteration of large veins leads to enlargement and snake-like tortuosity of veins of the collateral circulation on the thoracic and abdominal walls (Figure 1).

Budd-Chiari syndrome is a relatively common complication of BD and the presence of hepatic-vein thrombosis is one of the major prognostic factors affecting survival [6].

Involvement of the eye is a common cause of morbidity and it may lead to blindness. Eye involvement is bilateral in 90% of affected individuals. Eye manifestations include iritis, posterior and anterior uveitis, vasculitis, and optic neuritis. Uveitis, with hypopyon, is a hallmark of BD, occurs in 10% of patients.

Skin involvement can manifest as erythema nodosum, folliculitis, and acneiform skin eruptions. Erythema nodosum lesions tend to disappear in 10–14 days. Some pigmentation often follows the disappearance of the lesion. Increased irritability of the skin (pathergy test) in response to non-specific stimulations occurs in the majority of patients and the pathergy test is defined to be one of the diagnostic signs in the ISG criteria.

Arthralgia and arthritis are observed in slightly more than half the patients. The knee is the most frequently involved joint, while the ankle, elbow and wrist are more frequently involved compared to the small joints. In most instances the involvement is asymmetrical and recurrent, and rarely causes permanent joint damage.

Erosions and ulcers may also be present in the gastrointestinal system, which may lead to perforation and melaena. The terminal ileum and caecum are the sites of predilection. The most common lesions found in central nervous system are benign intracranial hypertension, pyramidal and brain stem involvement, and psychiatric disturbances. Motor rather than sensory...
neurological symptoms develop. Nervous system involvement is usually associated with a poor prognosis. Epididymitis occurs in 4.5 to 8% of male patients and it resolves within 1 or 2 weeks. The involvement of the kidney has recently been reviewed in this journal [7]. Other infrequent manifestations of involvement of the kidney has recently been reviewed in BD patients and it resolves within 1 or 2 weeks. The diagnosis. Epididymitis occurs in 4.5 to 8% of male patients. AA lesion is usually associated with a poor prognosis. Antineutrophilic cytoplasmic and antiphospholipid antibodies are elevated in a minority of BD patients [2]. There are no laboratory markers that correlate well with the clinical findings in BD.

**Laboratory findings**

Elevated serum mucoprotein, glycoprotein, and C-reactive protein concentrations, dysproteinemaia, leukocytosis, elevated erythrocyte sedimentation rate, and antibodies to human oral mucosa are common but non-specific laboratory findings. Antineutrophilic cytoplasmic and antiphospholipid antibodies are elevated in a minority of BD patients [2]. There are no laboratory markers that correlate well with the clinical findings in BD.

**Treatment**

There are few controlled studies reported on the management of BD. Because BD usually runs an undulating course of exacerbations and remissions, it is generally difficult to evaluate the efficacy of therapy. Treatment of BD is symptomatic and empirical and varies according to the clinical manifestations [9]. Although definitive data do not exist, there is a tendency among physicians to prescribe colchicine to all patients [9]. A double-blind, placebo-controlled, long-term clinical trial of colchicine for BD is under way. Topical preparations of local anaesthetics and local steroid preparations provide symptomatic relief and probably shorten the duration of oral ulcers. Local steroid preparations may alleviate minor symptoms of genital ulcers. Occasionally, major oral and genital ulcers may necessitate the use of systemic corticosteroids. Recently a randomized, double-blind, placebo-controlled trial has shown the efficacy of thalidomide in the management of mucocutaneous lesions [10]. Colchicine may be beneficial for the erythema nodosum and arthralgia. Simple analgesics, anti-inflammatory agents, and interferon-α have been used for the treatment of arthritis [2,9]. In a recent clinical trial, prophylactic benzathine penicillin with colchicine resulted in a reduction of episodes and prolonged the duration of episode-free intervals compared to the arm receiving colchicine alone [11]. Local corticosteroid-containing eye-drops and ointments are sufficient to control mild anterior uveitis, but severe eye involvement of recent onset in a young patient requires intensive treatment, such as a combination of systemic corticosteroids, azathioprine, and cyclosporin. A controlled, long-term study regarding the treatment of vascular BD has not yet been reported. Antiplatelet agents such as low-dose aspirin and diprydamole are recommended for venous involvement, but a controversy exists on this subject [5,9]. Routine anticoagulation with heparin or oral anticoagulants is not advised. Severe vasculitis in BD is treated with systemic corticosteroids and immunosuppressives as in other forms of vasculitis.

**Summary and conclusions**

Behçet’s disease is a vasculitic disorder in which the aetiopathogenetic pathway has not yet been clarified. Many organs and systems may be affected in BD. The causes of the wide-ranged clinical spectrum and the variable severity of involvement, including the kidneys remain to be defined. Behçet’s disease should also be considered in the differential diagnosis of AA amyloidosis as well as vasculitic connective-tissue disorders. Specific laboratory tests for the diagnosis and follow up are needed. Only clarification of the aetiopathogenesis of BD can lead to better treatment options.

**References**