BEHCET'S DISEASE - A REVIEW

MOHAMMED MOHY EL DIN SELIM, MD
Consultant Dermatologist

HASSAN ALI AL ABDULLA, MD
Chairman of the Department of Dermatology
Hamad Medical Corporation
Doha, Qatar.

The triple symptom complex of oral genital ulceration and relapsing uveitis is named "Behcet's Disease" (B.D.) after the Turkish dermatologist Huluci Behcet (1889-1948) who described the complex in 1937[1]. Ever since BD has been seen in many parts of the world and is reported to be more prevalent in the Mediterranean, Middle East and Japan. The prevalence rate per 100,000 population was found to be 10 in Japan[2], 190 in North Turkey[3], 6 in Britain[4], 5 in Minnesota - USA[5], 0.3 in Scotland[6] and was also reported in South African Blacks[7]. The disease usually affects adults 20-40 years of age[8] and is not uncommon in children and patients over 70 years old[9]. BD is more commonly seen in men with a male to female ratio ranging from 2 to 2.3 to 4.9:1[10,11]. In the Kingdom of Saudi Arabia (KSA) this male to female ratio was reported to be 3.4:1[12]. More than one member of the same family may be affected [13,14].

The past 6 decades witnessed the increase in reporting the relapsing manifestations of BD which included mucocutaneous lesion[15,16], ocular[17], neurologic[8,18,19,20], gastrointestinal[19,21,22,23,24], cardiopulmonary[25,26,27,28,29], muscles and joints[30], vascular[31,32,33,34] and genito urinary tract[35].

AETIOPATHOGENESIS

The aetiopathogenesis of BD which is not clearly understood involves genetic predisposition together with a defect in the humoral and or cell mediated immunoregulation. Some races are more prone to BD as in Turkey and Japan[13]. Genetic factors appear to be important and there is a significant association with HLA-B51[36]. In familial BD the association with HLA-B51 was 55%[14]. It was further delineated that BD is more closely associated with HLA-BW51 which is derived from HLA-B5 antigen[37]. In a Japanese family HLA-B51 was found in affected and non affected members and so it is likely that not only HLA but also other factors may be involved in pathogenesis of BD[38]. HLA-B51and HLA-B12 were more associated with mucocutaneous BD[39,40]. The HLA-B51 molecule itself may be responsible at least in part for the neutrophil hyperfunction seen in BD[41] because neutrophil hyperfunction was found in HLA-B51 in human phenotype regardless of the presence of the disease. HLA-B5 was more frequently associated with BD genital ulcers and also in occular BD[43,39] and its frequency was 92% in patients with family incidence of occular BD[42,39,43]. The association of HLA-B5 and HLA-B51 is 3 to 6 times more likely among Mediterraneans and Japanese[44,45]. HLA-B27 was more frequent in arthritic BD[39] which has to be differentiated from HLA-B27 positive patients with sacroileitis of Reiter's disease and entropathic arthritis. BD has not been found to link with HLA-DR or HLA-D antigen loci[8].

BD is classified as one of the artretides[46]. The underlying pathologic process in BD is a multifocal vasculitis involving veins, capillaries and arteries[31]. The vasculitis has been demonstrated in mucocutaneous lesions, cardio-pulmonary, gastrointestinal, renal, neural, skletal muscle and joint lesions. The morphologic appearance of the vasculitis varies from necrotizing vasculitis to lymphocytic vasculitis. The pattern is perhaps modulated by the susceptibility of the host and the shock organ, the environmental influences and other unidentified factors[31].

The host is genetically predisposed to BD and an abnormal humoral and or cell mediated immune reaction (CMI) may be initiated by antigens structurally homalogous to human antigen[47,48]. Such anti-

Correspondence:
Dr. M. M. Selim
Dept. of Dermatology and Venereology
Hamad Medical Corporation
P. O. Box 3050 - Doha - Qatar

gens include environmental microbial factors such as streptococcus pyogenes, streptococcus faecalis, streptococcus sanguis, streptococcus salvarius, herpes simplex virus type I, Epstein Barr virus and organic chemicals[16,47,49,50]. The antigens of the infectious agents are structurally homologous to mycobacterial Heat Shock Protein (HSP) of 65 KDa and to the endogenous autoantigens of the host which are produced under stress of heat or infection[16]. The microbial antigen with its HSP like structure penetrate to blood and lymphoid tissue leading to T cell sensitization and antibody production. It was found that sensitized T cells from BD patients respond to a greater degree when stimulated by HSP irrespective of HLA type[39].

Herpes simplex type I virus (HSVI) may be a triggering factor in BD as evidenced by the presence of its specific antibodies and the finding of the virus genome by polymerase chain reaction in T lymphocytes from patients with BD. Another evidence supporting the role of Herpes Simplex virus Type I in BD is the invitro hyperactivity of T8 suppressor cytotoxic cells taken from BD patients in response to herpex simplex antigens[40].

Study of the immunity status in 38 uveitis patients with BD revealed depressed lymphocyte proliferative response to mitogen in 58.8% of patients; hyperimmunoglobulinemia IgA & IgM in 63.3% and increased level of circulating immune complexes (CIC) in 78.3% and the presence of cryoglobulins in 57.1%. These results indicated infection of the patients with herpes virus, streptococcus and toxoplasmosis[51].

Other immunological studies demonstrated autoantibodies against oral mucosa and impaired function of T8 suppressor cells leading to increased B cell activity[52], reduced T helper cells[49], increased number of T8 cells[52], reduced T4/T8 ratio[49,53,] and lymphocytotoxic antibodies were detected [54].

Delayed hypersensitivity reaction to the group of streptococcal bacteria was found in BD. Biopsies taken from mouth ulcers and erythema nodosum like lesions of BD showed immunofluorescence to antistreptocccal group D antibodies in lesional vessel walls together with inflammatory infiltrate composed mainly of T cells, macrophages and natural killer cells (NK)[55]. NK cell number was found to be increased in active BD[56] but their function and their natural cytotoxicity was lower than in control group[57]. NK cell activity was augmented when alpha interferon was added to them and this suggests that in the active stage of BD a factor which activates NK cells is lacking[58].

The sensitized T-lymphocytes cross react with the epithelial autoantigens leading to cell mediated delayed immune hypersensitivity reaction with lymphocytotoxicity to the epithelial cells and initiate epithelial damage with the release of antigens which combine with autoantibodies forming immune complexes (IC). Autoantibodies to oral mucosa were found in 70-80% of BD patients[52]. Antibodies level to endothelial cells was reported to be high in BD[59]. Plasma endothelin-1 (ET-1) was significantly increased in active BD and its level correlates with disease activity [60].

The formed immune complexes (IC) lead either to:

A) Activation of complement leading to polymorphonuclear cell infiltration. C3 and C4 are reduced in the active stage while C9 and C- reactive proteins (CRP) are increased[47,48]. C9 may have a role in cell lysis. CRP modulate T cells and activate complement and promote phagocytosis.

B) Phagocytes fail to clear IC leading to accumulation of IC which will circulate leading to multifocal deposition of IC with activation of complement as in step(A). The titer of(CIC) may correlate with disease activity[61]. The multifocal damage seen in BD lesions is the result of CIC and cell mediated immune reaction (CMI)[61] and is characterized histopathologically by an early infiltration with T lymphocytes with production of cytokines (IL1,IL6,IL8 and Granulocyte Monocyte Colony Stimulating Factor GMCSF)[62,63,64] and promotion of tissue neutrophilia. The enhancement of neutrophil migration is due to a heat stable serum factor and the cytokines produced by cell mediated immune reaction and is related to HLA-B51[16].

Antineutrophil cytoplasmic autoantibodies were detected in BD patients[65,66]. There is also increased phagocytosis and increased release of lysosomal enzymes[3]. The antioxidant enzyme activity of PMN

is decreased leading to increased level of free oxygen[67], which causes tissue destruction with more production of autoantigens and more CIC. More than 50% of patients have high CIC and there is a relation between disease activity and the level of CIC in 50% of patients.

The histologic features of mucocutaneous lesions show predominant PMN cell vascular reaction and diffuse extravascular mononuclear cells with C3 deposited in blood vessels[36]. Jorizzo et al[15] stressed the importance of perivascular neutrophilic reaction around blood vessels as the only diagnostic finding that characterizes oral and genital aphthae and other skin lesions in BD as they are all variants of an immune complex mediated vessel based reaction[15]. In the same analysis Jorizzo et al found that specimens from pustular lesions in 14 out of 22 showed a varying degree of neutrophilic vascular reaction and only 3 out of 22 showed only mononuclear cell infiltrate in perivascular pattern and they suggested that this mononuclear cell reaction may represent an early stage in a later neutrophilic reaction. They suggested that histologic changes should be included as a diagnostic criterion for BD and that skin biopsy should be required[15]. The mononuclear cell vasculitic reaction with or without thrombosis may be predominantly lymphocytic. The neutrophilic vascular reaction has a sweet syndrome like pattern characterized by erythrocyte extravasation and no fibrin deposition. This histopathologic pattern has to be differentiated from sweet syndrome, pyoderma gangrenosum, idiopathic pustular vasculitis and bowel associated dermatoses syndromes. Vascular thrombosis independent of the degree of inflammation is frequently seen and blood high lipoprotein (a) level is a thrombogenic risk factor in BD[68]. Vascular thrombosis is attributed to antibody mediated endothelial injury and protein C or S deficiency, factor XII deficiency, inhibition of plasminogen activator and circulating lupus anticoagulant[47,53,69,70]. From these finding it is suggested that delayed hypersensitivity cell mediated immune reaction together with antigen antibody mediated cytotoxicity followed by accumulation of PMN cells have a role in pathogenesis of BD[55,56,57,58,59,62]. Fibrinolytic system may be involved in the development of BD. Nada et al 1992[53] stated that the increased level of fibrinogen and fibrinogen degradation products were found in BD and that fibrinolytic system abnormalities are most probably secondary event.

The mechanism underlying the production of BD may be summarized in the following points[39,40,47,48].

1. BD patients are genetically predisposed as suggested by the association of the disease with ceratin HLA antigens.

2. epithelial autoantigens are formed and cross react with environmental antigens which may be microorganisms, viruses or chemicals. These antigens trigger an immunologic reaction with formation of antibodies and sensitized lymphocytes. Cell mediated reaction occurs and initiate epithelial damage with the release of more autoantigens which combine with autoantibodies forming immune complexes (epithelial autoantigen or microbial cross reacting antigens —> sensitized lymphocytes and antibodies —> initiate epithelial damage —> release of antigens which combine with antibodies —> immune complex).

The occurence of cell mediated immune reaction is confirmed by

a) characteristic light and electron micro scopic histopathologic pattern
b) reduced natural killer cell activity and reduced T4/T8 ratio
c) lymphocytotoxicity to oral epithelium

3. Cytokines are released from monocytes (IL1, IL6, IL8, GHCSF, TNF) these cytokines recruite active PMN cells which causes vasculitis and tissue destruction with more release of antigens that combine with antibodies forming more IC.

4. Soluble immune complexes directly activate complement (C3a, C5a, C56789) leading to polymorph infiltration, cell lysis and oral ulcers. or

5. IC are not phagocytosed because of defective phagocytosis by PMN cells. IC accumulate and circulate and activate complement resulting in multi system lesions. The difference in size of CIC explains the multifocal involvement in BD. Light and electon microscopic immunofluorescent studies support the occurence of neutrophilic vasculitis and vessel damage (Type III immune reaction) in vasculitic lesions of BD.

Diagnosis of BD:

The clinical presentation of BD usually permits correct diagnosis:

The diagnostic criteria suggested by Mason and Barnes[71], the international study group[72] and research committee of Japan[73] may be used as guidelines for diagnosis of BD. These criteria in general should provide an acceptable level of sensitivity, specificity and good bases for definite diagnosis[74]. When we compare the criteria of the international workshop[72] (Table 1) with other 4 sets of diagnostic criteria published 1992[75] (Table 2) and the point scoring system suggested for BD diagnosis[10]. The diagnosis of BD was found to require:

1. According to the international group[72]: the presence of oral ulceration plus any two of
   a) genital ulceration c) typical skin lesion
   b) typical eye lesion d) positive pathergy

2. according to Mason and Barnes(table 2):
   a) 3 major or
   b) 2 major + 2 minor

3. according to the Japanese group(table 2):
   a) 4 major to diagnose complete BD
   b) 3 major or 2 major and 2 minor to diag nose incomplete BD

4. according to O Duffy(table 2):
   Oral or genital ulceration + 2 other major
5. according to Chang and Zhang(table 2)
   a) three major or 2 major plus 2 minor to diagnose complete BD
   b) Two major only or one major and 2 mi nor to diagnose incomplete BD

6) According to the arbitrary point scoring sys tem[10] fourteen to 22 points are needed to di agnose BD (Table 3).

In diagnosing BD non invasive diagnostic techniques are sometimes made use of to detect and find out the extent of life threatening systemic lesions particularly vascular and neurological involvement. Brain Single photon Emission Computed Tomography (SPECT), MRI may provide useful information about cerebral cortical, mid brain and Pons lesions in neuro Behcet[76,77]. Recent advances in the diagnosis of vasculo-Behcet's disease have been achieved by the use of radio-nucleotide venography for deep vein thrombosis and computed tomography for arterial lesions[78]. Doppler ultrasonic techniques and strain gauze plethysmography can accurately evaluate arterial occlusion[79], CT and MRI may depict vascular stenosis, obstruction and aneurysm in B.D.[80]. Digital subtraction angiography (DSA) is needed as it is important to diagnose small vessel lesions and valuate the degree and extent of the vasculitis[81] - Plasma thrombomodulin level is high in BD and its measurement may evaluate vasculitis lesions[82].

Clinical Picture of BD:

B.D. may begin at any site. The starting lesion represents a phase in wide-spread multisystem disorder. The first presenting lesion in BD may remain for days, months or years before another organ or other location or system is affected. The longer the follow up the greater will be the chance for additional organ or system affection. The lesions are not morphologically specific for BD and are seen in other diseases. The diagnosis of B.D. on the basis of such early stage lesion is difficult because of absence of specific diagnostic test. It is only when multiple lesions appear that the clinical presentation allows correct diagnosis. The incidence of the commonest lesions in B.D.[44] are oral ulcers 99%, genital ulcers 87%, eye affection 68%, skin lesions 69%, joint affection 44%, thrombophlebitis 24% and affection of CNS 10%.

Oral ulcers in BD are painful and recurrent at irregular intervals. It is considered the main diagnostic feature of BD. However 3% of patients may not have oral ulcers[32] and diagnosis of BD may be permitted in absence of oral ulcer[72]. Oral ulcers are described as:

Minor: small ulcers usually affecting the mucosa of the lips, cheeks and sides of the tongue. They last 4-14 days and recur at 1-4 months interval.

Major: are single large ulcers involving oropharynx, dorsum of tongue and last 10-30 days and heal with scarring and recur at less than monthly intervals.

Herpetiform: appear as numerous small ulcers grouped on oral mucosa and may coallesce to form single irregular ulcer and last from 7-14 days.

Oral ulcers are reported to be the first presenting sign of BD in 27% of cases[44] or 25-75% in other publication[8]. There is no difference in the clinical

appearance of Behcet's oral ulcers and recurrent aphthous ulcers, regarding the clinical appearance, duration, age of onset, frequency of recuurence and history of family incidence. Chronic recurrent aphthous mouth ulcers are more prevalent and are estimated to affect 10% of normal population while BD has much less incidence.

About 8-12% of patients with recurrent oral aphthous ulcers have iron or folate or B12 deficiency and 2% suffer from coeliac disease and 2 percent get the aphthae premenstrually.

However the increased number of ulcers, the concurrent variation in size from that of herpetiform to major ulcers and the involvement of the soft palate and pharynx together with the diffuse erythema around the ulcers are all pointers to Behcet's oral ulcers[83].

In absence of pathognomonic clinical picture and pathognomoniclaboratory tests[39] the histopathology of oral ulcers may have characteristic features of vasculitis which still overlaps with major categories of vasculitis[84] more over a positive biopsy is helpful but a negative one does not exclude the diagnosis of BD because the vasculitis may be focal and segmental.

Oral ulcers must be differentiated from other causes of mouth ulcers such as herpes simplex, Steven Johnson syndrome, recurrent aphthous stomatitis, pemphigus, lupus erythematosus, syphilis, lichen planus, pernicious anemia, Sjogren syndrome and rheumatoid arthritis. HLA-antigen typing may help in diagnosis[36,37,39].

It was found that the most common sign of BD in children is oral ulceration[9]. The average time between oral lesions in children and the second major manifestaiton was 8.8 years after which the third and fourth organs became affected within 1-2 years. So oral ulceratin should not be neglected in children[9].

In our experience one adult male (57 years old) kept having recurrent major aphthous ulcers every 2 weeks for 18 years before he showed occular, cutaneous vascular and neural manifestions of BD.

Cutaneous Lesions:

Skin lesions are reported to occur in 44-88% of patients and is the first sign in 5% of cases[15] In Kingdom of Saudi Arabia (KSA) skin lesions occurred in 57% of patients[12] and in children the skin lesions were reported to occur in 72.5% to 77.6% of children[9,85]. The skin lesions may be erythema nodosum like and is usually mainly in females, thrombophlebitis, pseudofolliculitis, papulopustular lesions, acneiform nodules in post adolescent patients not on steroid treatment, pyoderma, pyoderma gangrenosum, Sweet's syndrome, bullous eruption.

The skin lesions are more commonly found bilaterally on lower extremities. Acral purpuric papulo nodular lesions were reported[16] Henock Schoenlein purpura like rash was reported representing a flare up of BD[86].

Recurrent genital ulcers have the incidence of 87% of patients[44]. The ulcers may affect the scrotum, penis, perineal region in males and vulva and vagina in females. The ulcers are round circumscribed deep and painful. They may be 2-3 cm in diameter and heal leaving atrophic scar. They recur less frequently than oral ulcers. In children genital ulcers occur in 82.8% of affected children[85]. Genital ulcers are reported to be the first presenting sign of BD in less than 1% of patients[44].

Occular lesions:

Eyes are affected in 70-85% of BD patients[10]. They present as first sign of the disease in 29% of cases[44] but most cases are usually preceeded by other organs affected by several years. The incidence of eye affection is 65% in KSA[12] and is 27.5% in children[9]. Children uveitis represent 2-6% of all cases of uveitis in an ophthalmologic clinic and BD is among the systemic diseases which cause such uveitis[87]. The usual eye affection in BD is recurrent episodes of anterior and posterior non granulomatous uveitis, hypopyon, painful iridocyclitis and marked reduction of binoccular vision[8]. Other occular lesions that may occur are recurrent occlusive episodes of retinal veins, viterous haemorrhage, optic neuritis, optic nerve atrophy, cataract, secondary glaucoma, scleritis, keratitis and panophthalmitis[8].

Prognostic risk factors in patients with occulo BD

were studied by Sakamato et al[88]. Thirty two factors taken from clinical records were used to select statistically significant risk factors for visual loss. It was concluded that skin lesions, arthritis and posterior uveitis are linked to loss of vision while female sex, disease interval and anterior uveitis attacks are related to retainment of vision[88].

The damage caused by BD in the eyes is possibly due to cell mediated immune vasculitis and humoral immune mechanisms do not have a major role in the occular immunopathology[89]. Human T cell lines and clones specific to retinal antigens will provide the framework necessary to examine the events that lead to occular involvement and inflammation[89].

Skin Hyper-reactivity Response (Pathergy) in BD:

Pathergy or the development of pustular vasculitic lesions after non specific minor trauma to the skin is unique feature in B.D. The cutaneous pathergy in BD could be elicited by a needle prick or intracutaenous injection of saline or histamine and the result is read after 24-48 hours[90]. Pathergy was positive in 9 out of 11 and 45 out of 46 BD patients in Israel[91]. The cutaneous pathergy was elicited in 17.5% of patients in KSA[12], in 25-75% of patients in Japan and Turkey and was infrequent in North America and North Europe[3]. Pathergy test appears to be highly sensitive in diagnosis and follow up of BD[8]. Histopathologically there is PMN leucocyte infiltration followed by influx of large number of mast cells. The reaction is the result of augmented PMN chemotaxis. Histopathologic pathergy testing is a useful adjunct to the diagnosis of B.D.[92].

In a retrospective study of BD in our area 3 patients presented with skin pathergy long before the symptom complex of BD appeared. The first was a male patient who presented with acute swelling and inflammation of his hands 24 hours following fish fin prick and was diagnosed as erysipaloid. The second patient was a female who presented with cellulitis of her foot following a needle prick. The third patient was a female who wounded herself while shaving the suprapubic and perineal hairs. She developed a chancriform lesion on the labia majora at the site of the superficial injury. The diagnosis was only possible after other manifestation of BD became clinically manifest.

Other clinical criteria reported in BD include:-

1. Vascular lesions

The incidence of vascular lesions ranges betwen 7-29%. Four types of vascular leisons, in BD are recogniszed, arterial occlusion, aneurysms, venous occlusion and variceal development[93]. Vessels of any size can be affected veins more than arteries. Thrombophelebitis is a major manifestaiton of BD[20]. Reviewing the literature on vascular involvement of BD the most common lesions were subcutaneous thrombophlebitis and venous occlusion of upper or lower extremities[32]. Although vascular lesions are not mentioned among the major diagnostic criteria yet it was found that it occurs in 25% of patients[32]. In BD vascular involvement has been attributed to an antibody mediated endothelial injury, protein C or S deficiency, factor XII deficiency, inhibition of plasminogen activator and circulating lupus anticoagulant[16]. It is advisable to investigate BD patients who have venous thrombosis by estimating levels of protein C and S and anti thrombin III.

The artery most commonly affected is the aorta followed by the pulmonary artery, Virtually no artery, small or large is spared including coronary arteries. Two thirds of the lesions are aneurysms and the rest are occlusions[70,71]. Aneurysms of major arteries reported include aneurysm of aortic artery with massive incompetence of aortic valves[94], aortic regurgitation[95], superior mesenteric artery aneurysm[96], bilateral iliac artery aneurysm[97], pulmonary artery aneurysm[98,99]. The appearance of pulmonary artery aneurysm represent poor prognosis[100]. Slow progressive arterial involvement may occur in BD in absence of significant symptoms[101]. Rupture of arterial aneurysm is the leading cause of death in BD[79]. In KSA arterial thrombosis and aneurysm occured in 18% of cases and deep vein thrombosis in 18%[12].

Arteries may be affected by thrombo-occlusive episodes - occlusion of subclavian lead to pulseless disease, renal artery stenosis lead to hypertension, femoral artery stenosis lead to femer head necrosis and intermittant claudication.

2. Arthritic symptoms: (arthralgia, swelling, redness)

The symptoms are usually subacute self limiting and non deforming. It is linked with disease activity and is frequently associated with fever. The joints affected are the knees, ankles, elbows and wrists. Joint affection is seen in 44 to 60% of cases[44,10] and may be the presenting sign in 12% of cases[44]. Articular lesions are seen in 31.7% of children[85].

3. Gastro Intestinal lesion

Clinical symptoms of entero-Behcet's disease include, diarrhoea, constipation, abdominal pain, vomiting, melena, intestinal ulceration from vasculitis. In Scotland gastrointestinal affection (GIT) is seen in 50% of cases[6]. GIT affection amounted to 50% in children[85] and 4% in KSA[12]. Intestinal BD simulating Crohn's disease was reported[102]. Colitis in BD tends to localize in ileococcal region with deep ulceration. Perforated ileal ulceration with massive bleeding may occur due to intestinal angiitis, periphlebitis, venous thrombosis and end arteritis[103]. Erosions of the oesophagus, perforation of ulcer, oesophagitis and severe stenosis[21] and oesophageal varicies secondary to occlusion of both caval veins[104], small bile duct damage resembling sclerosing chalangitis with enteritis and pancreatitis due to vasculitis were reported in BD[105,22].

4. Neuro Behcet has the incidence of 18%[44] and represent 0.9% of total neurological admissions. Men are affected more than women and 81% presented with signs and symptoms indistinguishable from idiopathic intracranial hypertension and aseptic intracranial venous occlusive disease[106]. Usually neuro Behcet's disease appear 2 months to 27 years after the extra neural signs[107], but is reported to be the first presenting sign in 5-10%, of cases[44]. Two of our patients presented with meningo encephalitis (unpublished data). C.N.S. involvement in BD included meningo encephalitits, confusion, mental disorder which are related to secondary dysfunction of the frontal cortex due to damage of subcortical structure mainly the brain stem. Acute disseminated encephalomyelitis mimicking temporal lobe tumor. Neuro Behcet with facial palsy, gait disturbance, pathological reflexes and psychiatric symptoms, unilateral sensori neural hearing loss and bilateral hearing loss were reported in B.D.[108,109,110,111]. MRI and brain stem auditory evoked potentials are useful in detecting the presence and assessing the degree of neurologic involvement in Behcet's disease[15]. Evoked potential study in BD might be helpful to separate neuro Behcet's disease from other disorders with similar symptomatology and to disclose sub-clinical CNS involvement and to evaluate and monitor CNS disease activity and provide objective measures of treatment response[112].

5. Cardio Pulmonary

Intrathoraxic involvement includes thromboembolism of superior vena cava and or other mediastinal veins, aneurysm of aorta and pulmonary arteries, pulmonary infarction and haemorrhage, pleural effusion, rarely myocardial infarction, pericardial involvement and hilar or mediastinal lymphadenopathy. Angiography and venography should be avoided because aneurysm may develop at site of arterial puncture and veins get quickly thrombozed. CT and MR angiography are the imageing techniques of choice in B.D.[113]. Right ventricular thrombosis is also reported in BD[114] also congestive cardiomyopathy, left ventricular disabling dysfunction, endocarditis with affection of bicuspid or aortic valves, chylo-thorax and chylopericardium were diagnosed in BD secondary to thrombosis of superior vena cava, the innominate and subclavian veins[27].

6. Genito Urinary Tract

Kidneys may show asymptomatic focal glomerulonephritis and secondary amyloidosis. Epidydimitis, orchitis, ulceration of scrotum and penis, and urethro vaginal fistula were reported[35].

7. Occurence of myositis and the presence of a positive family history of oral ulcer or BD are considered as minor criteria.

Treatment of BD

Progress in treatment of BD depends on the increase of knowledge about its aetiopathogenesis, the new immunosuppressants, new antiinflammatory drugs, antithrombotic, anticoagulants and results of new treatment trials. Drugs that are currently used to treat BD are:-

1) **Steroids** have been used effectively in the

dose of 60 mg of prednisolone daily. Steroids may be required to control ophthalmic or neuro BD[39]. Steroids are used alone or in combination with immuno suppressive drugs which have beneficial effect and are steroid saving agents. The choice of immunosuppressive therapy is between alkylating agents and drugs that inhibit interleukin 2 production[115].

2. Methotrexate is usually given in combination with prednisolone. It has an immunomodulatory and an anti-inflammatory effect. It inhibits neutrophil chemotaxis, C5a induced inflammation and leukotriene B4 induced dermatoses. It inhibits the number of OKT6 dendritic cells in the epidermis and suppresses interleukin binding to T cell receptors. Methotrexate given in the dose of 15mg weekly with prednisolone resulted in improvement and prednisolone was tapered to zero and BD cleared in one year[116].

3. Azathioprine is given either alone or in combination with systemic steroid. It is given in the dose of 1- 2.5 mg/kg body weight per day[39,40]. It suppresses both cellular and humoral immunity and has an anti inflammatory effect. It has serious side effects as: liver cirrhosis, myelotoxicity and can induce sterility and opportunistic infection due to immunosuppression.

4. Cyclophosphamide (Cytoxan) is a derivative of nitrogen mustard. The recommended dose is 2-3 mg/kg body weight per day orally until leukopenia occured and then dose is reduced to maintenance therapy[40]. Pulse cyclophosphamide is given as 1 gm per meter square surface area of body intravenous once per month with 0.5 mg prednisolone per kg. body/weight per day. This treatment is reported to give significant results and is well tolerated[40].

5. Chlorambucil was recommended to treat BD in daily dose of 6-8 mg per day (0.1-0.2 mg/kg body weight/day). It is effective in occular, genital, oral, cutaneous and arthritic lesions of BD. In a series of patients treated with this drug for 2-18 years leukopenia occured in 59%, thrombocytopenia in 38%, major infection in 8%, malignancies in 8% and amenorrhoea in 63% of premenopausal women. The drug was discontinued after control of the disease in 68% of patients and because of lack of efficacy in 14%[40].

6. FK 506[117,118] is an immunosuppressive agent used to treat uveitis in BD. Five out of 8 patients improved. The major side effects were sensation of warmth, hypomagnesemia, renal dysfunction, glucose intolerance and disorders of CNS.

7. Cyclosporine A (CA) : It blocks synthesis and or release of IL1 from macrophages and IL2 from helper T cells. It has an immunosuppressive effect without myelotoxicity. CA when given in the dose of 5 mg per kg body weight per day for 24 months clinical remission occured in 87.5% of patients after 6-12 months[119].CA can be continued at low dose for unspecified time and if the disease does not resolve combination with low dose steroid should be considered[120]. Combined CA and prednisolone therapy is effective and less toxic than treatment with CA alone[121]. CA 5 mg/kg body weight/day combined with prednisolone 0.2-0.6 mg/kg body weight/day were given for 4-32 months (average 19.5 months). It is known that the higher the dose of CA the more rapid the improvement and the more apparent the benefit during treatment[122] and improvement is dose dependant.

Side effects of CA included rise of creatinine in 45% and in bilirubin in 27% and hypertension in 4.5% of patients. These side effects disappeared as dose was tapered[123] . Other side effects known are hirsutism, urea retension, gynaecomastia, and hypertrophy ofgums. Reactivation of the disease occurs when the drug is stopped or reduced[123].

CA 5mg/kg/day was tried versus cyclophosphamide 1 gram I.V. monthly.In the first 6 months visual improvement was better in CA treated group however the follow up of patients for 24 months suggested that the initial improvement in the first 6 months was not sustained[124].

There has been no evidence of a permanent drug induced remission of BD. For this reason and because CA can produce irreversible kidney toxicity, long term treatment must be cautiously done and well monitored. CA is a vasoconstrictor and a reduction in the renovascular tone after withdrawal of CA could increase renal blood flow and the glom-

erular filtration rate, such increases could lead to decline in serum creatinine level to normal in absence of anyreversal of tissue damage.

Renal biopsy after initiation of treatment by 13 months showed stripes of interstitial fibrosis with tubular atrophy and arteriolar alteration which is commonly associated with azotemia and twof o l d increase in serum creatinine concentration[122].

8. Interferon Alpha 2b

Interferon Alpha 2b was used to treat refractory occular BD[125,126]. Interferon alpha 2b is a glycoprotein produced by cell in response to viral infection. It has antiviral, immunomodulatory, antiproliferative and an antitumor properties. Treatment of BD with interferon alpha 2b starts with 3 million units given subcutaneous 3 times per week and gradually increased to 12 million units - a total dose of 216 million is reached in 2 months and 9 million is given once monthly. All patients became symptom free after 2 months[127].

9. Colchicine

It is an alkaloid isolated from the meadow Safron (autumn crocus, colchicum autuminale). It inhibits polymorphonuclear chemotaxis which is thought to be over active in BD. It also blocks the ability of serum to enhance neutrophil migration[47]. It is useful in treatment of BD in the dose of 1 mg/day for a period of 2 monthsto 2 years[39]. It may be given in the dose of 0.6mg 2/ day. One of t h e disturbing side effects is diarrhoea which may be accompanied by nausea, vomiting and abdominal pain. These side effects also occur after parenteral administration. Over dose may lead to burning throat pain, bloody diarrhoea, shock, hematuria, oligurea and ascending CNS depression. Colchicine affects the microtubules of PMN cells and leads to clinical improvement in cutaneous and occular lesions of BD including severe uveitis and gastrointestinal Behcet's manifestation[39,50,128].

10. Thalidomide

It is a useful therapeutic option to treat severe oral and genital ulceration that failed to respond to other treatments[129]. It is reported to cure BD associated with pyoderma gangrenosum[130]. The physician should be aware of the danger of axonal neuropathy and teratogenesis at all times during thalidamide therapy. Thalidamide is given in the dose of 200 mg/day and results in complete resolution of ulcers in 81% of patients within one month and 20% did not need further thalidomide treatment and the remainder were maintained on small daily doses of thalidamide ranging 7-200 mg.

Symptomatic neuropathy occured in 13.5% and a further 13.5% had asymptomatic neuropathy. The incidence of thalidamide neuropathy may be between 21-50%. Individual susceptibility with possible genetic predisposition seem to be more important than the daily dose and duration of thalidomide therapy[131].

Table (1)
Ref [72]
International criteria for Classification of BD

Recurrent oral ulceration (minor aphthous, major aphthous or herpetiform ulceration observed by a physician or reported reliably by patient)
Recurrent at least three times in one 12-month period
Plus 2 of

1) Recurrent genital ulceration
   Recurrent genital aphthous ulceration or scarring, especially males, observed by physician or reliably reported by patient.
2) Eye lesions
   Anterior uveitis
   Posterior uveitis
   Cells in vitreous on slit lamp examination
   or Retinal vasculitis observed by qualified physician (ophthalmologist)
3) Skin lesions
   Erythema nodosum-like lesions observed by physician or reliably reported by patient
   Pseudo folliculitis
   Papulopustular lesions
   or Acneiform nodules consistent with Behcet's disease - observed by a physician and in post-adolescent patients not receiving corticosteroids.
4) Positive pathergy test
   To be read by a physician at 24-48 h, performed with oblique. insertion of a 20-gauge or smaller needle under sterile conditions.

Other Lines of Treatment[39,41,128]

Transfer factor obtained from lymphocyte of healthy persons and given as subcutaneous injection caused improvement in 3 out of 5 BD patients[39]. Poliomyelitis vaccine bymouth, nonsteroidalanti inflammatoryagents,

prostacycline, Dap-sone, levamesole, Azelastine hydrochloride, ecozapen-taenoic acid, sulfapyridine, plasma exchange therapy, I.V. high doses of immunoglobulin G and acyclovir. Anticoagulants and fibrinolytic agents (ethylestrenol; phenformin, streptokinase, stanozolol) are beneficial in controlling deep vein thrombosis[79]. Prostaglandins, ticlopidine and low dose aspirin as an antiplatelet alleviate thrombophlebitis and erythema nodosum and reduce frequency of symptoms[39].

Table -2
Ref [75]

Manifestations of Disease	Mason & Barnes (1969)	Japanese (1987)	O'Duffy (1974)	Cheng & Zhang (1980)
Oral ulceration	Major	Major	Major	Major
Genital ulceration	Major	Major	Major	Major
Eye lesions	Major	Major	Major	Major
Uveitis + hypopyon	*	*	*	*
Iridocyclitis		*		
Chorioretinitis		*		
corneal ulceration	*			
retrobulbar neuritis	*			
Skin lesions	Major	Major	Major	Major
pustules	*			
ulceration	*			
erythema nodosum	*	*	*	*
erythema multiform	*			*
subcutaneous		*		
thrombophelebitis		*		*
hyperirritability (pathergy)		*		*
folliculitis/acne-like lesions				
Arthritis/arthralgia	Minor	Minor	Major	Minor
Gastrointestinal ulceration	Minor	Minor	Major	Minor
ileocaecal lesions		*		
colitis		*		
Vasculitis/thrombophlebitis	Minor	Minor	Major	Minor
large vessel arteritis		*	*	
CNS lesions	Minor	Minor	Minor	Minor
CVS lesions	Minor			
Epididymitis	Minor	Minor		Minor
Pulmonary - haemoptysis/fibrosis				Minor
Renal-ulceration/haematuria				Minor
Family history	Minor			
Diagnosis requires:	3 Major or 2 Major+2 Minor	C4 Major 13 Major or 2 Major+2 Minor	Oral or Genital Ulceration+2 other Majors	C3 Major or 2 Major+2 Minor I 2 Major 0r 1 Major+2 Minor

*Indicates specific features listed in the published diagnostic criteria set: C. 'complete' disease: I, 'incomplete' disease

COMPARISON OF DIAGNOSTIC CRITERIA SETS
BRITISH JOURNAL OF THE RHEUMATOLOGY

Conclusion:

After this review we find as previously stated by Chaple 1992[48] that Behcet's disease still retains its mysteries regarding its aetiopathogenesis, the lack of definitive diagnostic laboratory tests and the uncertain prognosis of its treatment.

TABLE - 3
Ref [10]

ARBITRARY POINT SCORING

SIGN	SCORE	SIGN	SCORE
Oral ulceration	4	CNS	2
Genital ulceration	4	Cardiovascular	2
Occular inflammation	4	Gastrointestinal	2
Retinal vasculitis	2	Kidney	1
Erythema nodosum	2	Lungs	1
Joint affection	2	Pathergy	1

REFERENCES :

1. Behcet H: Some observation on the clinical picture of the so called triple symptom complex. Dermatologica 1940; 8:73-8.

2. Shimizu T, Ehrlich GE and Inaba G: Behcet's Disease (Behcet's syndrome) Semin. Arthritis Rheum. 1979; 8:223-60.

3. Yazici H: Behcet's syndrome, a personal view. Clin. Exp. Rheumatol 1987; 5:1-3.

4. Chamberlain MA: Behcet's Disease B.M.J. 1978; 2:1369-70

5. O'Duffy JD: Vasculitis in Behcet's Disease. Rheum. Dis. Clin. North Am. 1990; 16:423-31

6. Jankowski J, Crombie I and Jankowski R: Behcet's sundrome in Scotland Postgrad. Med. J. 1992; 68:566-70.

7. Jacyk WK: Behcet's disease in South African Blacks: Report of 5 cases. J. Am. Acad. Dermatol 1994; 30 (5 pt 2): 869-73.

8. Stratigos AJ; LaskarisG and Stratigos JD: Behcet's disease seminars in Neurology 1992; 4:346-56.

9. Kim DK, Chang SN, Bang D, Lee ES and Lee S: The clinical analysis of 40 cases of childhood - Onset Behcet's disease. Paediatr. Dermatol. 1994; 11(2): 95-101.

10. Gerant DJ: Behcet's disease: Dermatology in General Medicine 1987 - Third Edition by Fitzpatrick, Eisen, Wolf, Freedberg and Austen - McGraw Hill book Company. P 1239-44

11. Kaplan RP and Ahmed AR: Behcet's syndrome: Clinical dermatology - Chief editor Joseph Dd - JB Lippincotte Company Philadelphia Twentieth Revision 1993 volume two unit 7-19 PP 1-13.

12. Al-Dalaan AN, Al-Balaa SR, El-Ramahi K, Al-Kawi Z, Bohliga S, Bahabri S and Al-Janadi MA: Behcet's disease in Saudi Arabia. J. Rheumatol 1994; 21(4): 658-61

13. Dundar SV, Gencalp U and Simsek H: Familial cases of Behcet's disease. Br.J.Dermatol 1985; 113: 319-21

14. Mori M, Kuriyama T, Mitsuda T, Aihara Y, Yokota S, Chiba J, Nagaoka S. Familial Behcet's disease a case report. Ryumachi 1994; 34(6): 988-92.

15. Jorizzo JL, Abernethy JL, White WL, Mangelsdorf HC, Zouboulis CC, Sarica R, Gaffney K, Mat C, Yazici H, Al-Ialaan A, Khalil SHA, Kaneko F and Jorizzo EAF: Mucocutaneous criteria for the diagnosis of Behcet's disease: an analysis of clinico pathologic data from multiple international center. J.Am.Acad. Dermatol 1995; 32: 968-76.

16. Magro CM and Crowson AN: Cutaneous manifestations of Behcet's disease Inter.J. Dermatol 1995; 14: 159-65.

17. Callen JP and Mahl CF: occulocutaneous manifestations observed in multisystem disorders. Dermatologic clinics 1992; 10: 709-16

18. Jongen PIH, Daelmans HEM, Bruneel B and den Hartog MR: Humoral and cellular immunologic study of cerebro-spinal fluid in a patient with Behcet's encephalitis. Arch. Neurol. 1992; 49: 1075-78.

19. Jiharo K, Abe J and Murakami T: Neuronal hyaline inclusions observed in an autopsy case of Behcet's disease. Acta Pathologica Japonica 1992; 42: 432-38.

20. Wechsler B, Vidailhet M, Piette JC, Bousser MG, Dell Isola B Belelry O and Godeau P: Cerebral venous thrombosis in Behcet's disease - clinical study and long term follow up of 35 cases. Neurology 1992; 42: 614-18.

21. Bottomley WW, Dakkak M, Walton S and Bennet JR: Eosophageal involvement in Behcet's disease - Is endoscopy necessary. Digestive diseases and sciences 1992; 37: 594-97

22. Huong DLT, Wechsler B, Dell Isola B, Lautier-Frau M, Palazzo L, Bletry O, Piette JC and Godeau P: Acute pancreatitis in Behcet's disease. Digestive diseases and sciences 1992; 37: 1452-53.

23. Bloxham CA, Henderson DC, Hampson J and Burt AD: Nodular regenerative hyperplasia of the liver in Behcet's disease. Histopathology 1992; 20:452-54.

24. Gedikoglu G; Demiriz M, Gunhan O, Somuncu I and Finci R: Enterocolitis in Behcet's syndrome. Eur.J. Surg. 1992; 158: 515-17.

25. Tunaci A, Berkmen YM and Gokmen E: Thoracic involvment in Behcet's Disease: Pathologic, clinical and imaging features. AJR 1995, 164:51-56.

26. Erkan F and Cavdar T: Pulmonary vasculitis in Behcet's disease. Am.Rev. Respir. Dis. 1992; 146:222-39.

27. Coplu L, Emri S, Selcuk ZT, Kalyoncu F, Balkanci F, Sahin AA and Boris YI: Life threatening chylous pleural and pericardial effusion in a patient with Behcet's syndrome. Thorax 1994; 47: 64-65.

28. Huraib S: Right atrial Thrombus as a complication of subclavian vein cathetarization - a case report. The Journal of Vascular Diseases 1992, 439-442.

29. Ozkan M, Emel O, Ozdemin M, Yurdakul S, Koca H, Ozdogan H, Hamuryudan V, Dirican A and Yazici H: M-Mode, 2-D and Doppler echocardiographic study in 65 patients with Behcet's syndrome. European Heart Journal 1992; 13:638-41.

30. Lingenfelser T, DuerkH, Stevens A, Grassmann T, Knorr M and Saal JG: Generalized myositis in Behcet's disease - Treatment with cyclosporine. Annals of Internal Medicine 1992; 116; 651-653.

31. Lie J.T.: Vascular involvement in Behcet's disease - arterial and venous and vessels of all sizes. The Journal of rheumatology 1992; 19: 341-43

32. Koc Y, Gullu I, Apek G, Akpolat T, Kansu E, Kiraz S, Batman F, Kansu T, Balkanci F, Akkaya S, Telatar H and Zileli T: Vascular involvement in Behcet's disease. The Journal of Rheumatology 1992; 19: 402-10

33. Hatzinicolaou P, Vayopoulos G, Mavropoulos S, Aessopos A, Stamatelos G, Sakellaropoulos N and Kaklamanis PH: Vascular manifestations in Behcet's disease. Br. J. Rheumatology 1991; 31: 284-85

34. Thomas I, Helmold ME and Mychay S: Behcet's disease presenting as superior vena cava syndrome. J. Am. Acad. Dermatol. 1992; 26: 863-65.

35. Monteiro H, Nogueira R and De Carvalho H: Behcet's syndrome and vesicovaginal fistula, an unusual complication. The Journal of urology 1995; 153: 407-8

36. Inoue C, Itoh R, Kawa Y, Mizoguchi M: Pathogenesis of mucocutaneous lesions in Behcet's disease. J. Dermatol 1994; 21: 474-80.

37. Ohno S, Ohguchi M, Hirosp S, Matsuda H, Wakisaka A, Aizawa M: Close association of HLA-BW-51 with Behcet's disease. Arch. Ophthalmol. 1982; 100: 1455-58.

38. Hayasaka S, Kurome H, Noda S: HLA antigens in a Japanese family with Behcet's disease. Graefes - Arch - Exp - Ophthalmol 1994, 232 (10): 589-90

39. Arbesfeld SJ and Kurban AK: Behcet's disese new perspectives on an enigmatic syndrome. J.Am. Acad. Dermatol 1988; 19: 767-79.

40. Jorizzo JL and Rogers RS: Behcet's disease an update based ont he international conference held in Rochester - Minnesota. Sept. 14 and 15 1989. J.Am.Acad. Dermatol 1990, 23: 738-41.

41. Takeno M, Kariyone A, Yamashita N, Takiguchi M, Mizushima Y, Kaneoka H, Sakane T: Excessive function of peripheral blood neutrophils from patients with Behcet's disease and from HLA-B51 transgenic mice. Arthritis Rheum. 1995; 38(3): 426-33

42. Azizleri G, Aksungur VL, Sarica R, Akyol E, Ovul C: The association of HLA-B5 antigen with specific manifestations of Behcet's disease. Dermatology 1994; 188 (4): 293-5

43. Nishiura K, Kotake S, Ichilshi A, Matsuda H: Familial occurence of Behcet's disease. Nippon-Ganka-Gakkai-Zasshi. 1944;98(6): 604-8

44. Chajek T, Fainaru M: Behcet's disease - Report of 41 cases and a review of the literature. Medicine (Baltimore) 1975; 54: 179-96

45. Ohno S, Nakayama E Suguira S et al specific histocompatibility antigens associated with Behcet's disease. Am.J. Ophthalmol 1975; 80: 636-41.

46. Parums DV: The artertides: Histopathology 1994: 25(1): 1-20.

47. Jorizzo JL, Solomon AR, Zanolli MD, Leshin B: Neutrophilic vascular reactions. J.Am.Acad. Dermatol 1988; 19: 983-1005.

48. Chaple C: Behcet's disease retains most of its mysteries. BMJ 1992; 304: 1199-1200.

49. Young C, Lehner T, Barnes CG: CD4 and CD8 cell responsers to herpes simplex in Behcet's disease. Clin. Exp. Immunol 1988; 73: 6-10.

50. Lehner T: The role of disorder in immunoregulation associated with herpes simplex virus type I in Behcet's disease. International Congress and symposium series No. 103. Royal Society of Medicine Services, London 1986: 31-41.

51. Teplinskaia LE, Kaliberdina AF, Zaitseva NS, Bulanova TD, Katsnelson La: Clinical-immunological disorders in uveitis in patients with Behcet's syndrome. Vestn-Oftalmol 1994; 110: 23-5.

52. Kaneko F, Takahashi Y, Muramatsu Y, and Muira Y: Immunological studies on aphthous ulcers and erythema nodosum like eruption in Behcet's disease. Br. J. Dermatol. 1985; 113: 303-12.

53. Nada M, El-Ashmawi SE, El-Anani G, El-Ansary M, El-Zawahry MB and Shaheen Z: Behcet's disease - A study of the immunology and fibrinolytic activity of the blood. J. Pan. Arab League ofDermatologists 1992; 3: 29-35.

54. Gunaydin I, Yazici H, Ozbakir F, Hamuryudan V, Yurdakul S. Lymphocytotoxic antibodies in the healthy children of patients with Behcet's syndrome. J. of Rheumatology 1992; 19:1996-98

55. Kaneko F, Takahashi Y, Murmatsu R, Adachi K, Muira Y, Nakane A and Minagawa T: Natural killer cell number and function in peripheral lymphoid cell in Behcet's disease. Br. J. Dermatol. 1985; 113: 313-18.

56. Onder M, Buzkurt M, Gurer MA, Gulekon A, Sezgin P, Imir T: Natural cellular toxicity in Behcet's disease. J. Dermatol. 1994; 21: 239-43.

57. Jonegen PIH, Daelman's HEM, Brunnel B and den Hartog MR: Humoral and cellular immunologic study of cerebrospinal fluid in a patient with Behcet's encephalitis. Arch. Neurol. 1992; 49: 1075-78.

58. Suzuki N, Sakane T, Ueda Y and Tsunemato T: Abnormal B cell function in patients with Behcet's disease. Arthritis Rheumatol. 1986; 29: 212-19.

59. Cervera R, Navarro M, Lopez-Soto A, Cid MC, Font J, Esparaza J, Reveter JC, Monteagudo J, Ingelmo M and Urbano Marquez A: Antibodies to endothelial cells in Behcet's disease: Cell binding heterogenity and association with clinical activity. Ann. Rheum. Dis. 1994; 53: 265-7.

60. Ural Au, Yalcin A, Beyan C, Isimer A and Bayhan H. Plasma endothelin - 1 concentrations in patients with Behcet's disease. Scand. J. Rheumatol 1994; 23: 322-5.

61. Jorizzo JL, Hudson D, Schmalstieg FC, Daniels JC Apisarnthanarax P, Henry JC, Gonzalez EB, Ichikawa Y and Cavallo T: Behcet's syndrome: Immune complexes, neutrophil migration and colchicine therapy. J. Am. Acad Dermatol. 1984; 10: 205-14.

62. Katayama T, Tachinami K, Ishiguro M and Kubota Y: The relation between Behcet's disease and interleukin - 1 beta production - Nippon - Ganka - Gakkal - Zasshi 1994; 98: 197-201.

63. Takashama H, Itoh R, Inoue - Komatsu C, Furusawa S, Takahashi - H and Mizugushi M: Granulocyte colony stimulating factor (GCSF) and granulocyte macrophage colony stimulating factor (GMCSF) in Behcet's disease. J. Dermatol. 1994; 21: 546-52.

64. Itoh R, Takenaka T, Okitsu-Negishi S, Matsushima K and Mizoguchi M: Interleukin 8 in Behcet's disease. J. Dermatol 1994; 21: 397-404.

65. Khan IH, Catto GR, Mc Leod AM: Antineutrophil cytoplasmic antibody associated vasculitis and renal failure in Behcet's disease (letter-comment). Nephrol.dial.Transplant. 1993; 8: 871-3.

66. Baleva M, Kolarov Z and Nikilov K: Antineutrophil cytoplasmic auto-antibody in two patients with Behcet's disease (letter) Nephrol-dial-Tranplant 1994; 9: 876.

67. Dogan P, Tanrikulu G, Soyuer U and Kose K: Oxidating enzymes of polymorphnuclear leukocytes and plasma fibrinogen, ceruloplasmin and copper levels in Behcet's disease. Clin. Biochem 1994; 27: 413-18.

68. Orem A, Deger O, Memis O, Caliskan K, Cimsit G: High lipoprotein (a) levels as a thrombogenic risk factor in Behcet's disease (letter). Ann.Rheum.Dis. 1994; 53: 351-2.

69. Shehto NM, Ghosh K, Abdul-kader B and Al-Assad HS: Extensive venous thrombosis in a case of Behcet's disease associated with heterozygous protein C deficiency. Thrombosis and Haemostasis F.K. Schattauer Verlagogesellschaft mbh (Stuttgart) 1992; 67: 283.

70. Chafa O, Fischer AM, Meriane F, Chellali T; Sternberg C, Otmani F and Benabadji M: Behcet Syndrome associated with protein S deficiency Thrombosis and Haemostasis F.K. Schattauer Verlagsgesselschaft mbh (Stuttgart) 1992; 67: 1-3.

71. Mason RM, Barnes CG: Behcet's syndrome with arthritis. Ann. Rheum. Dis. 1969; 28: 95-103.

72. International study group for Behcet's disease: Criteria for diagnosis of Behcet's disease. The Lancet 1990; 1078-80.

73. Behcet's disease research committee of Japan. Behcet's disease guide to diagnosis of Behcet's disease. Jpn. J. Ophthalmol. 1974; 18: 291-4.

74. Feutrie ML, Hachulla E, Hatron PY, Flipo RM, Brouillard M, Labalette P, Delaporte E, Wallaert B, Gosset D and Devulder B: Behcet's disease comparative aspect of diagnostic criteria Presse - Med 1994, 23; 1809-12.

75. The international study group for Behcet's disease: Evaluation of diagnostic (classification) criteria in Behcet's disease - Towards internationally agreed criteria. British Journal of Rheumatology 1992; 31: 299-308.

76. Watanabe N, Seto H, Sato S, Simizu M, Wu-YW, Kageyama M, Nomura K and Kakishita M: Brain SPECT with neuro-Behcet disease. Clin. Nuc. Med. 1995; 20: 61-4.

77. Arai T, Mizukami K, Sasaki M, Tanaka Y, Shiraishi H, Horiguchi H, Ogata T: Clinicopathological study on a case of neuro-Behcet's disease: in special reference to MRI, SPECT and neuropathological findings. Jpn. J. Psychiatry Neurol. 1994; 48: 77-84.

78. Hashimoto T and Haraoka H: Vaculo Behcet's disease. Nippon - Rinsho 1994; 52: 2138-42.

79. Ysuda K, Miyatake T, Murashita T; Sakuma M: Physiological diagnostic techniques of patients with vasculitis. Nippon-Rinsho 1994; 52: 2060-5.

80. Niimi H, Nakajima Y, Nosaka S, Kuroki K, Tsukamoto H, Yamaguchi T, Ohyama Y, Ishikawa T: CT and MRI findings of refractory vasculitis. Nippon-Rinsho 1994; 52: 2047-53.

81. Yamada I, Himeno Y, Suzuki S: Angiography in vasculitis. Nippon-Rinsho 1994; 2041-6.

82. Ohdama S, Takano S, Miyake S, Kubota T, Sato K and Aoki N: Plasma thrombomodulin as a marker of vascular injuries in collagen vascular diseases. Am. J. Clin. Path. 1994; 101: 109-13.

83. Main DMG and Chamberlain MA: Clinical differentiation of oral ulceration in Behcet's disease. Br. J. Rheumatol. 1992; 31: 767-70.

84. Sugiura H and Hosoda Y. Histopathological and immunohistochemical diagnosis of intractable vasculitis syndromes. Nippon-Rinsho 1994; 52: 2034-40.

85. Mori M, Shimizu C, Kuriyama T, Ibe M, Mitsuda T, Aihara Y, Yokota S: Behcet's disease in childhood - case reports and review of the literature Ryumachi - 1994; 34: 34-41.

86. Golan G, Beeri R, Mevorach D: Henoch-Schonlein purpura - like disease representing a flare of Behcet's disease (letter). Br. J. Rheumatol 1994; 33: 1198-9.

87. Dufier JL, Yi E, Tiret A, Prieur AM: Occular involvements in chronic inflammatory diseases in children. Rev. Prat. 1994; 44: 2573-6.

88. Sakamoto M, Akazawa K, Nishioka Y, Sanui H, Inomata H, Nose Y: Prognostic factors of vision in patients with Behcet's disease. Ophthalmology 1995; 102: 317-21.

89. Charteris DG, Champ C, Rosenthal AR, Lightman SL: Behcet's disease activated T lymphocytes in retinal perivasculitis: Br. J. Ophthalmol. 1992; 76: 499-501.

90. Gilhar A, Winterstein G, Turani H, Landau J, and Etzioni A: Skin hyperreactivity response (Pathergy) in Behcet's disease. J. Am. Acad. Dermatol 1989; 21: 547-52.

91. Friedman-Birnbaum R, Bergman R and Aizen E. Sensitivity and specificity of pathergy test results in Israeli patients with Behcet's disease. Cutis: 1990; 45: 261-64.

92. Jorizzo JL, Solomon AR, Cavallo T: Behcet's syndrome immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow up. Arch. Pathol. Lab. Med. 1985; 109: 747-51.

93. Kuzu MA, Ozaslan C Koksoy C, Gurler A, Tuzuner A: Vascular involvement in Behcet's disease: 8 Year audit. World J. Surg. 1994; 18: 948-53.

94. Napoleone CP, DiPartolomeo R, Pierangeli G and Pierangeli A: Aneurysm in Behcet's disease an unusual association. Cardiovascu. Surg. 1994; 2: 379-80.

95. Hayase S, Yano Y, Ogawa K, Fujita K, Yuasa T, Kidokoro H, Hattori T: A case of aortic valve regurgitation associated with Behcet's disease. Kyobu-Geka 1994; 47: 408-12.

96. Men S, Ozmen MN, Balkanci F, Boyacigil S, Akbari H: Superior mesenteric artery aneurysm in Behcet's disease. Abdom. Imaging 1994; 19: 333-4.

97. Haabegaard A, Rordam P, Roder OC: Bilateral iliac artery aneurysms in a Behcet-like disease. Ugeskr-Laeger 1994; 156: 5711-2.

98. Puckette TC, Jolles H, Proto AV: Magnetic resonance imaging confirmation of pulmonary artery aneurysm in Behcet's disease. J. Thorax imaging 1994; 9: 172-5.

99. Uh-S, Kim Jo, You YK, Moon SH and Park CS: A case of

Behcet's disease combined with pulmonary artery aneurysm in a Korean female patient. Korean J. Intern. Med. 1994; 9: 47-50.

100. Numan F, Islac C, Berkmen T, Tuzun H and Cokyuksel O: Behcet's disease, pulmonary arterial involvement in 15 cases. Radiology 1994; 192: 465-8.

101. Cooper AM, Naughton MN, Williams BD: Chronic arterial occlusion associated with Behcet's disease. Br. J. Rheumatol 1994; 33: 170-2.

102. Masugi J, Matsui T, Fujimori T and Maeda S: A case of Behcet's disease with multiple longitudinal ulcers all over the colon. Am. J. Gastroenterol 1994; 89: 778-80.

103. Hamza M, Eleuch M, Kchir N, Zitouna M: Ileal perforation in 3 cases of Behcet's disease. Ann. Med. Intern. Paris 1994; 145: 99-102.

104. Orikasa H, Ejiri Y, Suzuki S, Ishikawa H, Miyata M, Obara K, Nishimaki T and Kasukawa R: A case of Behcet's disease with occlusion of both caval veins and "downhill" oesophageal varices. J. Gastroenterol 1994; 29: 506-10.

105. Hisaoka M, Haratake J, Nakamura T: Small bile duct abnormalities and chronic intrahepatic cholestatis in Behcet's syndrome. Hepatogastroenterology 1994; 41: 267-70.

106. Najim Al Din AS, Mubaidin A, Wriekat Al and Alqam M: Risk factors of aseptic intracranial venous occlusive disease. Acta Neurol Scan. 1994; 90: 412-6.

107. Samoud A, Jebnoun S, Souid M, Samoud S en-Dridi MF. Neurologic Behcet's disease. Arch. Pediatr. 1994; 12: 162-5.

108. Hasegawa H; Bitoh S, Koshino K, Obashi J, Iwaisako K and Fukushima Y: Acute relapsing disseminated encephalomyelitis (ARDEM) mimiking a temporal lobe tumor No-shinkei-Geka 1994; 22: 185-8.

109. Inagaki T, Ishino H, Seno H, Iijima M, Fujimoto A, Manou M, Harada T: A case of neuro-Behcet Disease with numerous hypertrophied and proliferated dendrites in the inferior olivary nucleus. No - To - Shinkei 1994; 46: 1177-83.

110. Smith LN: Unilateral sensorineural hearing loss in Behcet's disease. Am. J. Otorhinolaryngol. 1994; 15: 286-8.

111. Igarashi Y, Watanabe Y, Aso S: A case of Behcet's disease with otologic symptoms. ORL.J. Otorhinolaryngol - Relat. Spec. 1994; 56: 295-8.

112. Stigsby B, Bohlega S, Al-Kawi MZ, Al-Dalaan A, El-Ramahi K: Evoked potential findings in Behcet's disease - Brain stem autitory, visual and somato sensory evoked potentials in 44 patients Electroencephalogr - Clin - Neurophysiol. 1994; 92: 273-81.

113. Tunaci A, Berkmen YM, Gokmen E: Thoracic involvement in Behcet's disease: Pathologic, clinical and imaging features. AJR - AM - J. Roentgenol 1995; 164: 51-6.

114. Mendes LA, Magraw LL, Aldea GS, Davidoff R: Right ventricular thrombus: An unusual manifestation of Behcet's disease. J.Am.Soc. Echocardiogr. 1994; 7: 438-40.

115. O Duffy JD: Behcet's disease. Curr. Opin. Rheumatol. 1994; 6: 39-43.

116. Jorizzo JL, White WL, Wise CM, Zanolli MD and Sherertz EF: Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behcet's disease. J.AM.Acad.Dermatol. 1991; 24: 973-8.

117. Ishioka M, Ohno S, Nakamura S, Isobe K, Watanabe N, Ishigatsubo Y, Tanaka S: FK506 treatment of non infectious uveitis. Am.J. Ophthalmol. 1994; 15: 723-9.

118. Igarashi T, Ishigatsubo T, Ohno S, Ueda A, Okubo T, Tanaka S, Katsumata Y, Sakane T, Ohno S: Central nervous system toxicity related to FK 506 in patients with Behcet's disease (Letter). Ann. Rheum. Dis. 1994; 53: 350-1.

119. Pacor ML, Biasi D, Lunardi C, Cortina P, Caramaschi P, Girelli D, Botto M, Urbani G, Lombardo Gand Bambara LM: Cyclosporin in Behcet's disease: results in 16 patients after 24 months therapy. Clin. Rheumatol 1994; 13: 244-7.

120. Atmaca LS and Batioglu F: The efficacy of cyclosporin A in the treatment of Behcet's disease. Ophthalmic. Surg. 1994; 25:321-7.

121. Whitcup SM, Salvo EC Jr. and Nussenblatt RB: Combined cyclosporine and corticosteroid therapy for sight threatening uveitis in Behcet's disease. Am.J. Ophthalmol. 1994; 15: 39-45.

122. Fathman CG and Mayers BD: Cyclosporine therapy for autoimmune disease. The new Engl.J. of Medicine 1992; 326: 1693-94.

123. Sajjadi H, Soheilian M, Ahmadieh H, Hassanein K, Parvin M, Azarmina M, Ehyaee V and Amiransari B: Low dose cyclosporin-A therapy in Behcet's disease. J. Ocul. Pharmacol 1994; 10: 553-60.

124. Ozyazgan Y, Yurdakul S, Yazici H, Tuzun B, Iscimen A, Tuzun Y, Aktunc T, Pazarli H, Hamuryudan V and Muftuoglu A: Low dose cyclosporin A versus pulsed cyclophosphamide in Behcet's syndrome: a single masked trial. Br. J. Ophthalmol. 1992; 76: 241-43.

125. Durand JM and Soubeyrand J: Interferon alpha 2b for refractory occular Behcet's disease (letter, see comment) - Lancet 1994; 344 (8918):333.

126. Feron EJ, Rathova A, Van-Hagen PM, Baarsma GS and Suttorp - Schulten MS: Interferon alpha b2 for refractory occular Behcet's disease (letter Sec, comment) Lancet, 1994; 344(8918): 333.

127. Alposy E, Yilmaz E and Basaran E: Interferon therapy for Behcet's disease. J.Am.Acad.Dermatol 1994; 31: 617-19.

128. Hashimoto T and Takenchi A: Treatment of Behcet's disease Current Opinion in Rheumatology 1992; 31-34.

129. Gardner Medwin JM, Smith NJ and Powell RJ: The clinical experience with thalidomide in management of severe oral and genital ulceration in conditions such as Behcet's disease: Use of neurophysiological studies to detect thalidomide neuropathy. Ann. Rheum. Dis. 1994; 53: 828-52.

130. Rustin MHA, Gilkes JJH and Robinson TWE: Pyoderma gangreonosum associated with Behcet's disease: Treatment with thalidomide. J. Am. Acad. Dermatol. 1990; 23: 941-44.

131. Ochonisky S, Verroust J, Bastuji-Garin S, Gherardi R and Revuz J: Thalidomide neuropathy incidence and clinico-electrophysiologic findings in 42 patients. Arch. Dermatol. 1994; 130: 66-9.