BEHÇET'S DISEASE: AN OVERVIEW

ESEN KARAMURSEL AKPEK, M.D.

ABSTRACT

PURPOSE/METHODS:

Behçet's Disease is a multisystem inflammatory illness characterized by intraocular inflammation, oral and mucosal ulcerations, skin lesions, and a variety of other disorders involving multiple organs in the body. Complications of this vasculitis can lead to blindness and death. We discuss, herein the diagnosis and management of a patient with Behçet's Disease who presented with uveitis associated with retinal vasculitis.

CONCLUSION: Behçet's Disease is a rare systemic vasculitic disease that affects young people. It is a chronic disease with remissions and exacerbations that "burn out" after approximately 10 years of activity. Ocular involvement is common and visual prognosis is poor if the patient is not treated properly. CNS and gastrointestinal involvement, which are less common, may lead to death. The diagnosis of the Behçet's Disease is made on the basis of clinical criteria. The use of immunosuppressive and cytotoxic agents are mandatory in the successful treatment of the ocular and CNS manifestations of this vasculitis of unknown etiology.

INTRODUCTION

Behçet's Disease (BD) is a chronic, relapsing, occlusive vasculitis affecting almost every organ systems in the body. The disease is named after a Turkish dermatologist professor, Hulusi Behcet who in 1937 recognized recurrent iridocyclitis with hypopyon, aphthous lesions in the mouth, and ulceration of the genitalia in two patients (1). It occurs more frequently in the Middle East and Japan, but in fact BD is seen worldwide. As yet the cause of BD is unknown, but histopathologic features suggest that the tissue damage is caused by the associated vasculitis and immune complex deposition within the blood vessel wall, together with the activation of the complement system (2). Patients with BD should be treated only by physicians who are expert in the use of immunosuppressive and cytotoxic agents and who are expert in the recognition and treatment of dangerous side effects.

CASE REPORT

A 32 year old Greek dentist presented in May 1996 with a chief complaint of decreased visual acuity. His past ocular history revealed a diagnosis of retinal telangiectasia in his right eye 2 years ago.

His visual acuity was 20/70 OD and 20/40 OS. Intraocular pressures were within normal limits and slit lamp examination revealed 1/2 + and 1/4 + cells in the anterior chambers of OD and OS, respectively.

Fundus examination disclosed 1+ vitritis and retinal vasculitis of the right eye with soft exudates and intraretinal hemorrhages located nasal to the disc. There was also a moderate amount of cystoid macular edema. The fundus of the left eye was normal. (Figures 1a and 1b)

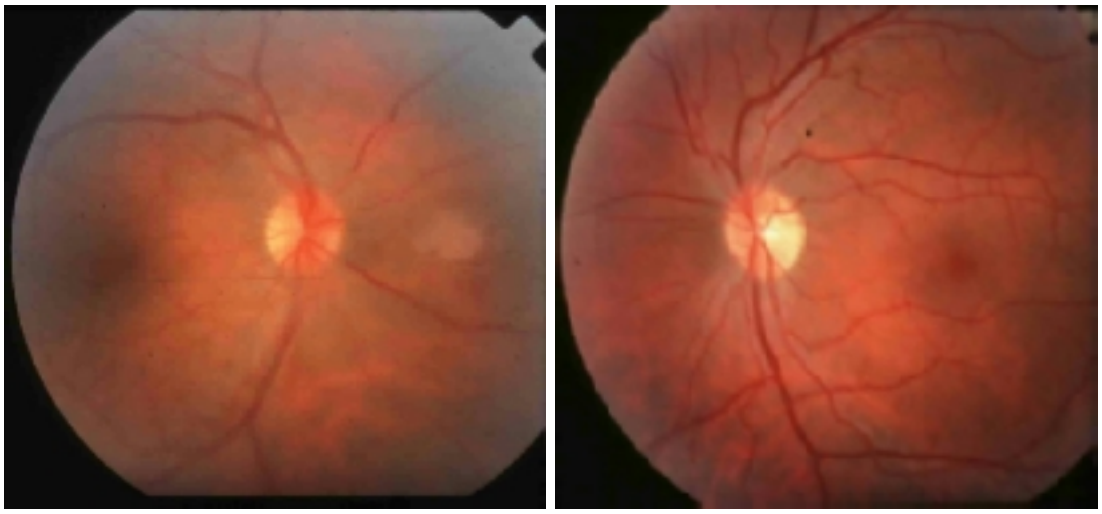

Figure 1a ********** **Figure 1**b

Fluorescein angiography confirmed cystoid macular edema and revealed leakage of the dye from the papillary vessels in the right eye and normal findings in the left eye (Figures 2a and 2b).

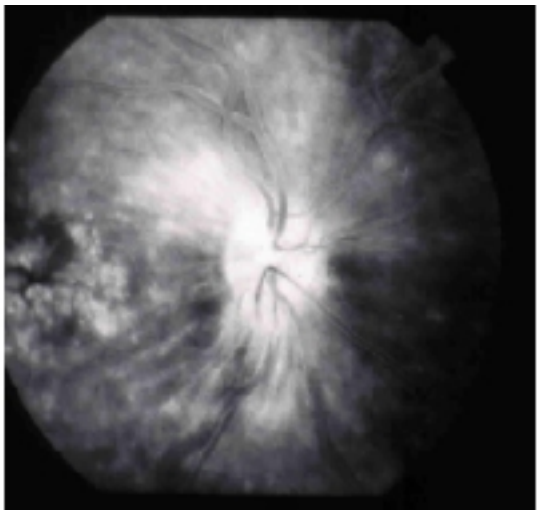

Figure 2a ********** **Figure 2**b

At this time the past history of the patient disclosed recurrent oral and genital ulcers since the age of 14. With these features (recurrent oral-genital ulcers and uveitis with retinal vasculitis) our diagnosis was Behçet's Disease (BD).

Laboratory investigations revealed leukocytosis, increased C-reactive protein, and increased soluble interleukin-II receptor levels. At this point we started the patient on systemic cyclosporin (100 mg tid), Imuran (50 mg tid), and prednisone (60 mg qd).The patient responded well to treatment and his vision increased and the fundus findings improved.

In September the patient's vision was remarkably better (20/32 OD and 20/20 OS), there was no active inflammation in any area of the eye and active papillitis had completely resolved (Figures 3a and 3b).

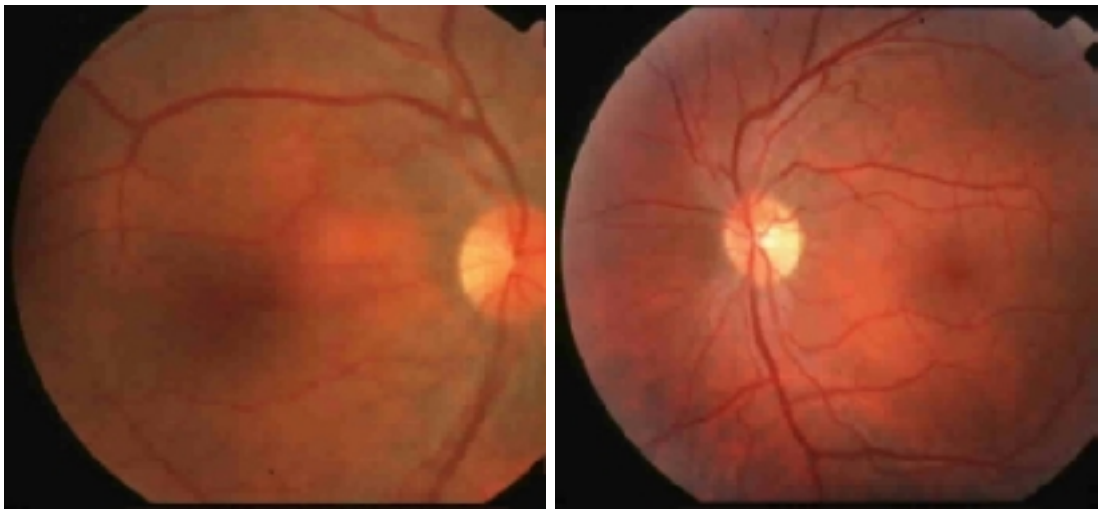

Figure 3a ********** **Figure 3**b

Fluorescein angiography revealed residual leakage from the papilla and decreased macular edema compared to the previous visit (**Figure 4**). The oral prednisone was tapered.

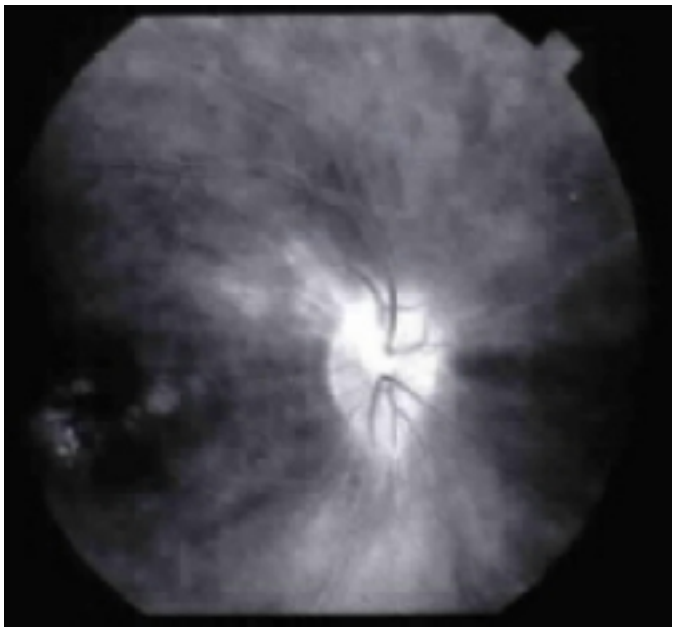

Figure 4

As of his last follow-up visit, on October 4, 1996, the patient was well tolerating his low dose cyclosporin and Imuran.

DISCUSSION

Behçet's Disease (BD) is a chronic, relapsing, occlusive vasculitis affecting multiple organ systems. The disease is named after a Turkish dermatologist professor Hulusi Behcet who in

1937 recognized recurrent iridocyclitis with hypopyon, aphthous lesions in the mouth, and ulceration of the genitalia in two patients (1).

BD is common in the Middle and Far East along the latitudes 30 to 45 degrees north in Asia and the Mediterranean basin, which corresponds to the Old Silk Route used by traders from the East to Europe (2).

BD is the leading cause of endogenous uveitis and one of the major causes of acquired blindness in the Middle East and in Japan. It is most common in Turkey and Japan, with prevalences 80-300/100 000 and 7-8.5/100 000, respectively (3,4). In the United States the prevalence is 0.4/100 000 (5), and BD represents 0.2 to 0.4 percent of uveitis cases in this country (6).Many reports have suggested that the disease is more common in males (6). More recent evidence , however, suggests a more even distribution of the disease between the sexes (7).

The mean age at onset is 25 to 35 years worldwide, with a range of 2 months to 72 years. More cases of BD in children have been reported recently (8).

In 1973 Ohno reported a strong association between BD and HLA-B5 (9).In a collaborative study of British and Turkish populations, Yazici and Chamberlain confirmed frequent HLA-B5 among Turkish patients with a relative risk of 7.5, but not in British patients (10).

BD is a multisystem inflammatory illness characterized by intraocular inflammation, oral and mucosal ulcerations, skin lesions and a variety of other disorders involving almost every organ system in the body.

The Behcet Disease Research Committee, organized by the Ministry of Health and Welfare of Japan, proposed a Guide for the Diagnosis of Behcet Disease which has been used throughout the world (11). The committee classifies the symptoms into major and minor diagnostic criteria (Table I). Lesions involving the joints, intestines and the CNS are called the minor criteria with respect to their importance in making a diagnosis of BD, but some of the minor criteria can be troublesome or life threatening for some patients.

TABLE I. Diagnostic Criteria For Behçet's Disease
(Proposed By The Behçet's Disease Research Committee of Japan)

MAJOR CRITERIA	MINOR CRITERIA
Recurrent Oral Aphthous Ulcers	Arthritis
Skin Lesions: **Erythema nodosum-like lesions **Folliculitis	Epididymitis
Genital Ulcers	Gastrointestinal Involvement
Ocular Disease: **Iridocyclitis with hypopyon **Posterior Uveitis with retinal vasculitis	Vascular Involevement: **Thrombophlebitis
	Neurologic Symptoms

Diagnosis:

Complete	Presence of all major criteria

Incomplete	3 major criteria 2 major + 2 minor criteria ocular disease + 1 major criterion ocular disease + 2 minor criteria
Suspect	2 major criteria
Possible	1 major criterion

The International Study Group for Behcet Disease proposed another set of diagnostic criteria in 1990 (12). Although there are basic similarities between these two criteria, the Behcet Disease Research Committee places more importance on ocular findings, whereas the International Study Group gives more emphasis to the presence of oral aphthous ulcers in confirming the diagnosis (Table II).

TABLE II. Diagnostic Criteria For Behçet's Disease Proposed By The International Study Group For Behcet Disease

Recurrent oral ulceration + 2 of the following:

1-Recurrent genital ulceration
2-Ocular involvement
3-Skin lesions
4-Positive pathergy test

SYSTEMIC FINDINGS

Recurrent aphthous stomatitis is a " sine qua non " of BD, and is usually the first systemic manifestation. They are typically round, sharply defined, painful and usually localized on the lips, gingiva, buccal mucosa, tongue and less commonly on the palate, tonsils and pharynx. They usually heal within 7 to 10 days (13).

Genital ulcers in male patients may appear on the scrotum and penis; in female patients lesions can develop on the vulva or vagina. They tend to be deeply located and often scar. An examination of the genital region can therefore be diagnostically useful in a suspected BD patient (13).

Other skin lesions typical of BD include erythema nodosum on the anterior surface of the legs, acneiform lesions or pseudofolliculitis on the backs and faces of the patients, and migratory thrombophlebitis (14). Another dermatologic feature of the BD is the positive pathergy test. In this test a sterile skin prick is performed with a sterile needle. The presence of marked redness and swelling, or a pustular lesion 24 to 48 hours later is interpreted as a positive result. Among American and Western Europian patients the positivity rate is extremely low. Among Turks it is positive in 79 % of patients with vascular system disease and 56 % in patients without vascular disease, indicating a significant association of positive pathergy test with vascular involvement (15).

At least half of the patients are affected by non-migratory, non-destructive arthritis. It usually reflects the level of systemic disease activity and is occasionally linked to ocular lesions.

Vasoocclusive inflammatory changes with aneurysm or thrombus formation can affect vessels of all sizes and can be life threatening. CNS manifestations of BD can be global or focal and can cause sensory, motor, or neuropsychiatric symptoms. Meningoencephalitis is the most common form of CNS involvement.

OCULAR FINDINGS

Ophthalmic involvement can be the presenting symptom of BD. A review of a Japanese patient population suggests that ocular involvement is more common in males (83 to 95 %) than in females (67 to 73 %), and that the incidence of ocular symptoms as the initial manifestation of BD is higher in male (24.5 %) than in female (8.6%) patients (16). Also CNS involvement with its potentially fatal sequela correlates with ocular involvement. Although unilateral ocular manifestations do occur, ocular involvement is usually bilateral, often asymmetric.

The classic finding in ocular BD is recurrent, sterile hypopyon described by Behcet, and it is a dramatic finding that is easily detected by non-ophthalmic physicians. However it only occurs in 1/3 of cases (16). The patient complains of periorbital pain, redness, photophobia, and blurred vision. Slit-lamp biomicroscopy shows conjunctival and ciliary injection, with aqueous flare and cells. Fine keratic precipitates are present on the corneal endothelium. The attack lasts 2 to 3 weeks, then subsides. But recurrences are the rule, with subsequent iris atrophy and posterior synechia formation.Rare anterior segment findings include corneal immune ring opacity, conjunctival ulcers, episcleritis and scleritis (17, 18).

The classic fundus finding is the necrotizing, obliterative retinal vasculitis affecting both arteries and veins in the posterior pole (7). Vascular sheathing with perivascular exudates, arteriolar attenuation, venous dilatation and tortuousity, and branch and central retinal vein occlusion are common posterior pole findings. Vitritis is always present during the acute phase.

Fluorescein angiography is useful in determining the extent of retinal and disc vasculitis. Typically there is leakage of dye from the small venules. In a recent Turkish study fundus angiographic abnormalities were found in 93 % of cases with BD. In the same study abnormal leakage of dye from peripheral retinal capillaries and venules was found in 6 % of patients who had no visual complaints as well as no abnormal findings on fundus exam (19).

Cataract formation is the most common anterior segment complication after recurrent inflammation, occurring in upto 36 % of cases (20). It was reported that the post-operative visual acuity was found to be significantly lower in eyes with BD than in those with idiopathic uveitis because of the severe posterior segment complications, mainly optic atrophy (21). Posterior synechiae, iris atrophy, and peripheral anterior synechia may develop during the course of repeated ocular inflammatory attacks. Peripheral anterior synechia or iris bombÕ from pupillary seclusion may cause secondary glaucoma. Retinal atrophy with optic atrophy is the end result of repeated episodes of posterior segment inflammation.

PATHOLOGY AND PATHOGENESIS

The ocular histopathologic changes are basically identical to those occurring in other organs , that is necrotizing, leukocytoclastic obliterative vasculitis which is probably immune complex mediated and affects both arteries and veins of all sizes.

During acute inflammation, the ciliary body and choroid show diffuse infiltration with neutrophils. During remission, infiltration with lymphocytes and plasma cells is seen. In late, chronic stages, there is proliferation of collagen fibers, sometimes with formation of a cyclitic membrane thickening of the choroid and sometimes hypotony and Phthisis bulbi.

Tissue damage in BD is caused by aberrant HLA-DR expression, immune complex deposition within the blood vessel wall and activation of complement system and vasculitis. Abnormalities of neutrophil functions, such as enhanced migration and generation of free radicals, and elevated levels of circulating activated T lymphocytes have been reported (22, 23). Sakane and associates reported a defect in the T-lymphocyte-mediated suppressor system and alterations in the

CD4/CD8 ratio of circulating cells of patients with BD, which can be explained by an increase in the CD8 fraction of T-lymphocytes (24). IL-8 levels were found to be higher in patients with active BD in a recent study, and since IL-8 has a potent effect on neutrophils, they concluded that this cytokine most likely participates in the inflammatory response of this disease (25).

LABORATORY INVESTIGATIONS

There are no laboratory findings specific for BD,and therefore careful assessment of a patient's clinical findings and history are critical for diagnosis. Patients may have high ESR, CRP or increased numbers of peripheral leukocytes during the active stages of the disease.

The presence of autoantibodies or extremely high values of immunoglobulin are not compatible with a diagnosis of BD; instead they suggest collagen vascular disease.

The pathergy test can be useful, and in fact it is one of the criteria suggested by ISG.

DIFFERENTIAL DIAGNOSIS

In patients with the incomplete form of BD or with an atypical presentation it is important to consider other forms of uveitis in the differential diagnosis.

In systemic lupus erythematosus, the retinal vasculitis is in the form of obliterative arteriolitis. The retinal vasculitis of BD tends to be hemorrhagic rather than obliterative and involves arteries and veins. The appearance of the retina in BD can be similar to the appearance of viral retinitis; in both processes there is patchy retinal infarction. Retinal infiltrates in BD do not progress to coalesce, and hemorrhagic vascular occlusion and the presence of branch retinal vein occlusion are not typical of viral retinitis. The hypopyon associated with HLA-B27 associated uveitis is less mobile than BD associated hypopyon because of the increased fibrinous reaction and it is usually unilateral. Systemic vasculitic diseases should also be considered in the differential diagnosis.

TREATMENT

Topical steroids and cycloplegics or periocular steroid injections can be used when ocular inflammation is confined to the anterior segment.

If there is posterior segment involvement in BD, systemic therapy is required. The choice of medications is determined by the severity of the disease. In general the treatment of the ocular form of the disease must be more aggressive when the patient has complete BD with neurologic and vascular involvement, multiple recurrences of uveitis, male sex, bilateral involvement, origin in the Mediterranean area or Far East (16). The most commonly used anti-inflammatory drugs are corticosteroids, cytotoxic agents, cyclosporine, and colchicine.

Corticosteroids:
Systemic corticosteroids have a rapid and definite anti-inflammatory effect in all phases of ocular BD, but especially in the acute phase. However these drugs failed to prevent visual deterioration and the ultimate blindness from the consequences of ocular BD (6, 7, 26). Still, steroid therapy; oral (1-1.5 mg/kg/day) or intravenous (1 gr/day for 3 days), or both, forms an important component in the plan of care for the patients with BD. In posterior segment inflammation, oral corticosteroids are used in combination with immunosuppressive drugs, and then the steroids are gradually tapered. The advantage of this regimen is to obtain benefit from the immediate Corticosteroid anti-inflammatory action while waiting for the full effect of the cytotoxic drug's action, which usually takes 3 to 6 weeks.

In chronic cases, maintenance doses (15-30 mg/day) of prednisone may be required in combination with immunosuppressives.

Chlorambucil:
Chlorambucil was the first cytotoxic drug to be used in the care of patients with ocular BD and it is still commonly used as the most efficacious single agent. The mode of action of this slow-acting alkylating agent is similar to that of cyclophosphamide. The usual starting dose is 0.1 mg/kg/day. A favorable response may take 1 to 3 months to become evident. Subsequently the drug dose is reduced, and a maintenance dose is given for 1 to 2 years depending on the symptoms, ocular findings, bone marrow tolerance, often special aspects of the individual.Chlorambucil therapy can be complicated by precipitous and persistent pancytopenia, amenorrhea, infection, and secondary malignancy (27). Malignancy later in life is a significant concern in patients receiving greater than 1300 mg in toto of chlorambucil (28). Pivetti-Pezzi and associates reported that early intervention with chlorambucil produced a better outcome than did corticosteroid therapy (29). A high dose short-term chlorambucil regimen for BD has also produced a favorable outcome (30). In contrast, Tabbara reported that the long-term results with chlorambucil were not particularly encouraging, with 75 % of eyes having a visual acuity of 20/200 or less when this agent was used as the sole therapy (31).

Cyclophosphamide:
Cyclophosphamide has been used widely in Japan with considerable efficacy in preventing the ocular attacks and maintaining good visual acuity for long periods (32). It has been used successfully in cases refractory to chlorambucil (7). It is a fast-acting alkylating agent which can be administered orally (1 mg/kg/day) or intravenously (750-1000 mg/m2/day every 4 weeks) with a potential kidney and bladder toxicity.

Azathioprine:
Azathioprine is a purine analogue, and it is usually used in combination therapy. Recently it was reported that oral azathioprine
(2.5 mg/kg/day) decreased recurrences of ocular BD (33). We generally use it in combination with cyclosporin and low dose prednisone.

Cyclosporin:
Cyclosporin is not cytotoxic and therefore presumably cannot induce clonal deletion of autoaggressive cells. It is relatively selective in inhibition of T-lymphocytes. In randomized studies, cyclosporin was found more effective for prevention of BD ocular recurrences than was colchicine and cyclophosphamide (34, 35). In a study done by Nussenblat et al cyclosporine was found to be effective in ocular BD, but the dose employed (10 mg/kg/day) was associated with significant renal toxicity (36). A recent study from Turkey suggested an initial dose of 5 mg/kg/day cyclosporin be used in the treatment of ocular BD, and if the intraocular inflammation does not totally resolve at this dosage or if the inflammatory process recurs, a combination of the cyclosporin with low doses of steroid should be considered (37). Cyclosporin therapy is generally limited to bilateral sight threatening cases of BD. Serum creatinine and creatinine clearance must be followed closely. It should be noted that abrupt discontinuation may lead to "rebound" phenomenon. As mentioned above, our bias here, if cyclosporin or Imuran are to be used, is to use them together, along with prednisone, in a manner similar to solid organ transplant rejection prevention therapy.

Tacrolimus:
Tacrolimus (FK 506) is a newly developed immunosuppressive drug with an immunologic activity very similar to cyclosporin. It binds to alpha 1 acid glycoprotein in serum and selectively inhibits CD 4+ T-lymphocytes. Japanese FK 506 Study Group on Refractory Uveitis reported favorable effects in 75 % of 53 patients with refractory uveitis, including 41 with BD (38). Recently subcutaneous interferon alpha was successfully used in patients with mucocutaneous disease and ocular involvement (39, 40).

Plasmapheresis induces rapid remission but does not prevent relapse or change the final outcome of the ocular inflammation (41).

There are also reports on pentoxifylline (42) and thalidomide (43) used in the care of patients with BD.

EYE SURGERY

Surgery is indicated whenever visual improvement can be expected and the eye has been free of inflammation for a minimum of 3 months. Operating on eyes with cataract and uveitis has been previously reviewed by Foster and associates (44). Their recommendations for a successful cataract surgery and for minimizing the postoperative uveitis are as follows:

Uveitis should be inactive for at least 3 months preoperatively, systemic and topical steroids should be used prophylactically for 1 week preoperatively and continued post operatively, immunosuppressive drugs should be continued, complete removal of cortical material should take place, and one piece PMMA posterior chamber intraocular lens should be used if the patient and the surgeon understand the special nature of this surgery, its risks, and the prognosis for success.

Laser photocoagulation in some patients is indicated, primarily to forestall vitreous hemorrhage and the development of neovascular glaucoma, as well as to decrease macular edema resulting from vein occlusion.

In a study from Turkey it was reported that the photocoagulation therapy for BD was well tolerated and successful in closing retinal capillary non-perfusion areas and eliminating retinal neovascularization (45).

PROGNOSIS

The systemic prognosis is good in patients with BD in the absence of CNS involvement or involvement of the major vessels. The disease itself generally goes into remission after approximately 10 years of activity.

In a study from Lebanon 75 % of the patients who were untreated or treated with steroids, lost vision to no light perception in a mean of 3.5 years(46). In an Israeli report of patients with ocular BD at 6 to 10 year follow-up, 10 % of eye had visual acuity of 20/40 or better, 16 % 20/50 to 20/100, 18 % were 20/200 to 20/400, 26 % were count fingers or less, and 30 % had no light perception (47).

In a recent study from Japan, it was reported that despite immuno-suppressive therapy, 35 % of the patients lost 5 or more lines of visual acuity or became legally blind in 3 years (48). It was also reported that male sex, posterior segment involvement, and frequent attacks are among the poor prognostic factors.

In a series from the USA, the visual prognosis is better. In a study from our service at Massachusetts Eye and Ear Infirmary, only 2 of 29 (7 %) patients and 12 of 58 (21 %) eyes had vision of 20/200 or less after a mean follow-up of 4 years (1-8 years) (49).

Although not commonly employed in clinical practice for BD, it was suggested that flash electroretinography together with pattern visually evoked potentials were good indicators for visual prognosis as well as for monitoring posterior segment changes (50).

REFERENCES

1- Behcet H. Uber rezidivierende, aphthose, durch ein Virus verursachte Geshwure am Munde, am Auge und an den Genitalien. Dematologische Wochenschr 1937;36:1152-1157
2- Levinsky RJ, Lehner T. Circulating immune complexes in Behçet's Syndrome and recurrent oral ulcers. J Lab Clin Med 1981;97:559
3- Mishima S, Masuda K, Izawa Y et al. Behçet's Disease in Japan: ophthalmologic aspects. Trans Am Ophthalmol Soc 1979;77:225-279
4- Yazici H. Behçet's Disease. In Klippel JH, Dieppe PA, editors. Rheumatology, 6.20.1-6.20.6, London 1994, Mosby
5- O'Duffy JD. Behçet's Disease. In Kelley WN, Harris ED Jr, Ruddy S, Sledge CB (eds). Textbook of Rheumatology, Philadelphia, WB Saunders, 1985, pp 1174-1178
6- Chajec T, Farinaru M. Behcet's Disease: Report of 41 cases and a review of the literature. Medicine 1975;54:179
7- Baer JC, Raizman MB, Foster CS. Ocular Behçet's Disease in the United States. Clinical presentation and visual outcome in 29 patients. In Masahiko U, Shigeaki O, Koki A (eds). Proceedings of the Fifth International Symposium on the Immunology and Immunopathology of the Eye , Tokyo, 13-15 March 1990. New York, Elsevier Science, 1990, p383
8- Ammann AJ, Johnson A, Fyfe GA, et al. Behcet' Syndrome. J Pediatr 1985;107:41
9- Ohno S, Aoki K, Sugiura S, et al. HLA-B5 and Behçet's Disease. Lancet 1973
10- Yazici H, Chamberlain MA, Schieuder I, et al. HLA antigens in Behçet's Disease. A reappraisal by a comparative study of Turkish and British patients. Ann Rheum Dis 1980;39:344-348
11- Mizushima Y, Inaba G, Mimura Y, et al. Guide for diagnosis of Behçet's Disease, report of Behçet's Disease Research Committee, Japan, 1987, Ministry of Health and Welfare
12- International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's Disease. Lancet 1990;335:1078-1080
13- Nakae K, Masaki F, HashimotoT, et al. A nationwide epidemiological survey on Behçet's Disease, report 2: association of HLA-B51 with clinic-epidemiological features, report of Behçet's Disease Research Committee, Japan, 1992, Ministry of Health and Welfare, pp 70-82
14- Ersoy F, Berkel, A, Firat T, et al. HLA antigens associated with Behçet's Disease. In Dausset J, Suejgaard A, (eds): HLA and disease, 100, Paris, 1976, PUB
15- Koc Y, Gullu I, Akpek G, et al. Vascular involvement in Behçet's Disease. J Rheumatol 1992;19:402-410
16- Mishima S, Masuda S, Izawa Y, et al. Behçet's Disease in Japan: Ophthalmologic aspects. Trans Am Ophthalmol Soc 1979;77:225
17- Cohen S, Kremer I, Tiqva P. Bilateral corneal immune ring opacity in Behçet's Syndrome. Arch Ophthalmol 1991;109:324-325
18- Olivieri I, Genovesi-Ebert F, Signorini G, Pasero G. Conjunctival ulceration in Behçet's Syndrome. Ann Rheum Dis 1992;51(4):574-579
19- Atmaca LS. Fundus changes associated with Behçet's Disease. Graefe's Arch Clin Exp Ophthalmol 1989;227:340-344
20- Hooper PL, Rao NA, Smith RE. Cataract extraction in uveitis patients. Surv Ophthalmol 1990;35:120-144
21- Ciftci OU, Ozdemir O. Cataract extraction comparative study of ocular Behçet's Disease and idiopathic uveitis. Ophthalmologica 1995;209:270-274
22- Jorizzo JL, Solomon AR, Canolli MD, Leshin B. Neutrophilic vascular reactions. J Am Acad Dermatol 1988;43:783
23- Niwa Y, Mizushima Y. Neutrophil-potentiating factors released from stimulated lymphocytes: Special reference to the increase in neutrophil-potentiating factors from streptococcus-stimulated lymphocytes of patients with Behçet's Disease. Clin Exp Immunol 1990;79:353
24- Valesini G, Pivetti-Pezzi P, Manstrandea F, et al. Evaluation of T cell subsets in Behçet's Syndrome using anti-T cell monoclonal antibodies. Clin Exp Immunol 1985;60:55-60
25- Al-Dalaan A, Al-Sedairy S, Al-Balaa S, et al. Enhanced interleukin 8 secretion in circulation of patients with Behçet's Disease. J Rheumatol 1995;22:904-907
26- Mamo JG, Bagdasarian A. Behçet's Disease: A report of 28 cases. Arch Ophthalmol

1964;71:38
27- Matteson EL, O'Duffy JD. Treatment of Behçet's Disease with chlorambucil. Proceedings of the International Congress on Behçet's Disease, Rochester, MN, 1989, p575
28- Travis LB, Curtis RE, Stoval M, et al. Risk of leukemia folloving treatment for non-Hodkin's lymphoma. J Natl Cancer Inst 1994;86(19):1450-1457
29- Pivetti-Pezzi P, Gasparri V, De Liso P, et al. Prognosis in Behçet's Disease. Ann Ophthalmol 1985;17:20-28
30- Tessler HH, Jennings T. High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's Disease. Br J Ophthalmol 1990;74:353-357
31- Tabbara KF. Chlorambucil in Behçet's Disease: A reappraisal. Ophthalmology 1983;45:265-268
32- Hijikata K, Masuda K. Visual prognosis in Behçet's Disease: Effects of cyclophosphamide and colchicine. Jpn J Ophthalmol 1978;16:284-329
33- Yazici H, Pazarli H, Barnes C, et al. A controlled trial of azathioprine in Behçet's Syndrome. N Engl J Med 1990;322:281
34- Masuda K, Nakajima A. Adouble masked study of ciclosporin treatment in Behçet's Disease. In Schindler R, ed. Ciclosporin in autoimmune diseases, Berlin, Springer-Verlag, 1985, pp162-164
35- Ozyazgan Y, Yurdakul S, Yazici H, et al. Low dose cyclosporin A versus pulsed cyclophosphamide in Behçet's Syndrome: A single masked trial, Br J Ophthalmol 1992;76:241-243
36- Nussenblat RB, Palestine AG, Chan CC, et al. Effectiveness of cyclosporine therapy for Behcet's Disease. Arthritis Rheum 1985;28:672
37- Atmaca LS, Batioglu F. The efficacy of cyclosporin A in the treatment of Behçet's Disease. Ophthalmic Surg 1994;25(5):321-327
38- Mochizuki M, Masuda K, Sakane T, et al. A clinical trial of FK 506 in refractory uveitis. Am J Ophthalmol 1993;115:763-769
39- Alpsoy E, Yilmaz E, Basaran E. Interferon therapy for Behçet's Disease. J Am Acad Dermatol 1994;31:617-619
40- Kotter I, Eckstein A, Zierhut M. Therapy of ocular manifestations in Behçet's Disease with interferon alpha. Invest Ophthalmol & Vis Sci 1996;37(3):1036
41- Raizman MB, Foster CS. Plasma exchange in the therapy of Behçet's Disease. Graefe's Arch Clin Exp Ophthalmol 1989;227:360
42- Yasui K, Kobayashi M, et al. Succesful treatment of Behcet's Disease with pentoxifylline. Ann Intern Med 1996;124(10):891-893
43- Gardner-Medvin JM, Smith NJ, Powell RJ. Clinical experience with thalidomide in the management of severe aral and genital ulceration in conditions in conditions such as Behcet's Disease: use of neurophysiological studies to detect thalodomide neuropathy. Ann Rheum Dis 1994;53(12)828-832
44- Foster CS, Fong LP, Singh G. Cataract surgery and intraocular lens implantation in patients with uveitis. Ophthalmolgy 1984;96:281
45- Atmaca LS. Experience with photocoagulation in Behçet's Disease. Ophthalmic Surg 1990;21(8):571-576
46- Mamo JG. The rate of visual loss in Behçet's Disease. Arch Ophthalmol 1970;84:451-
47- Ben Ezra D, Cohen E. Treatment and visual prognosis in Behçet's disease. Br J Ophthalmol 1986;70:589
48- Sakamato M, Akazamak K, Nishioka Y, et al. Prognostic factors of vision in patients with Behçet's Disease. Ophthalmology 1995;102:317-321
49- Foster CS, Baer JC, Raizman MB. Therapeutic responses to systemic immune suppressive chemotherapy agents in patients with Behçet's Syndrome affecting the eyes. Proceedings of the Fifth International CONGRESS on Behçet's Disease, Rochester, MN, 1989. In O'Duffy JD, Kokmen E (eds):Behçet's Disease; Basic and clinical aspects. New York, M Dekker, 1991, pp581-588
50- Cruz RD, Adachi-Usami E, Kakisu Y. Flash electroretinograms and pattern visually evoked cortical potentials in Behçet's Disease. Jpn J Ophthalmol 1990;34:142-148

QUESTIONS

1- Which is not a major criteria of Behcet's Disease according to Behcet's Disease Research Committee of Japan?

a- Recurrent aphthous ulcers
b- Erythema nodosum
c- Genital ulcers
d- Hypopyon iridocyclitis
e- Pathergy test

answer is e Ref:Jpn J Ophthalmol 1974;18:282

2- Which one is wrong related to Behcet's Disease uveitis?

a- Classic finding in ocular Behcet's Disease is iridocyclitis with hypopyon
b- Fine KPs are present on the corneal endothelium
c- Hypopyon may change with position and can form and dissappear rapidly
d- More common presentation is iridocyclitis without hypopyon
e- Typically iris atrophy and posterior synechia are not seen
answer is e Ref: Trans Am Ophthalmol Soc 1979;77:225

3- Which one is wrong related to posterior pole findings seen in Behcet's Disease:

a- The classic fundus finding is retinal vasculitis affecting only the arteries
b- Yellow-white exudates may form deep in the retina
c- Branch or central retinal vein occlusion may be present
d- Optic nerve involvement is usually in the form of papillitis
e- Macular edema is seen especially after recurrent attacks

answer is a Ref: Proceedings of the fifth international symposium on the immunology and immunopathology of the eye, Tokyo, 13-15 March 1990. New York, Elsevier Science, 1990, p 383

4- Which one is true related to FA findings seen in Behcet's Disease:

a- FA is mandatory in the care of Behcet's Disease patients
b- During acute inflammation, there is dilatation of retinal capillaries with dye leakage
c- Affected vessels in the retina and optic nerve leak the dye profusely in early transit
d- Commonly there is a loss of a clearly defined capillary free zone
e- All of the above

answer is e Ref: Graefe's Arch Clin Exp Ophthalmol 1989;227:340-344

5- In Behcet's Disease, the treatment of the ocular form of the disease must be more aggressive when the following conditions except one are present:

a- Multiple recurrences of uveitis
b- Neurologic and vascular involvement
c- Complete Behcet's Disease
d- Female sex
e- Retinal and bilateral involvement

answer is d Ref: Trans Am Ophthalmol Soc 1979;77:225