THE NEW ARMENIAN MEDICAL JOURNAL
Vol.4 (2010), N 2, p. 28-33

NEW TREATMENT OPTIONS FOR OCULAR BEHCET DISEASE

Malayan A.S., Hovakimyan A.V., Martirosyan S.S.

S.V. Malayan Ophthalmologic Center, Ministry of Health of the Republic of Armenia, Yerevan, Armenia

Abstract

Ocular Behcet disease has a distinctly high incidence among the population of Armenia, especially among the young patients. Behcet disease is a multi-system inflammatory illness characterized by intraocular inflammation, oral and genital ulcerations, skin lesions (erythema nodosum-like lesions, acneiform lesions or folliculitis, thrombophlebitis, cutaneous hypersensitivity) and a variety of other disorders, involving multiple organ systems of the body (joints, the intestine, epididymis, the vascular, and the central nervous system). Behcet disease is characterized by recurrent episodes of inflammation involving one or more organ systems. Generally, the onset of these episodes is sudden. Inflammation then subsides over a period of several weeks. The disease usually develops 2 to 3 years after the initial lesions of Behcet disease, which in most patients are oral aphthous ulcerations. Although the disease can affect the anterior and posterior parts of the eye separately, the majority of patients have panuveitis or posterior uveitis.

Ocular Behcet disease is the major cause of acquired blindness among uveitis patients in Armenia and the best medication for treatment of the disease is considered to be Cyclosporine (Sandimune, Neoral), which unfortunately is not affordable for the majority of our patients. Hence, it is important to find a new method of treatment of ocular Behcet disease.

Our study has shown that combination of Imuran (Azathioprine) (1.5-2.0 mg/kg/day) and Colchicine (1.0 mg/kg/day) associated with multiple subtenon injections of Diprospan 1.0 (Bethametasone) is dramatically effective in oculo-Behcet patients.

Keywords: *Behcet disease, uveitis, Imuran, Colchicine, Diprospan.*

INTRODUCTION

Behcet disease is named afer Hulusi Behcet. Although this disease was probably known to the ancients (Hippocrates described a disease quite similar to the one we now call Behcet disease). Behcet's 1937 report of this entity engendered enormous interest in the disorder [*Behcet H., 1937*]. The disease, though found worldwide, has a distinctly high incidence among certain groups of people. The entity is more common in Turkey, Japan, countries of Mediterranean basin, and in areas extending through the Middle East into Iran. The prevalence rate has been reported as 80 to 300 per 100,000 in Turkey and 7 to 8.5 per 100,000 in Japan [*Mishima S. et al., 1979; Shimizu T. et al., 1979; Yurdakul S. et al., 1988; Yazici H., 1994*].

Address for Correspondence:
S.V. Malayan Ophthalmologic Center
30 Fuchik Street, Yerevan 0054, Armenia
Tel.: (+374 93) 41 81 71; (+374 91) 33 93 04 (mob.)
E-mail: ahovakimyan@yahoo.com; svetlanadoc@mail.ru

There is no evidence that the disease is either increasing or decreasing is frequency. It has been suggested that Behcet disease, or at least an immunogenetic predisposition to it, was distributed throughout the ancient world by merchants who plied the old silk trading routes.

Many reports have suggested that the disease is more prevalent in males. However, more recent evidence suggests a more even distribution of the disease between the sexes. Although the discrepancies in reported male to female ratios might reflect a change in the nature of the disease, it is more likely that in previous years women in many countries were embarrassed to see a physician with complaints related to the cluster of signs and symptoms that make up Behcet disease. Male patients, as well as young individuals 15 to 25 years of age, experience a more protracted and severe form of the disease [*Yazici H. et al., 1984*].The disease has an interesting distribution even within countries where

it is prevalent. The disorder occurs more frequently in patients living in the northern parts of Japan than in those from the southern areas. As there is no known HLA or other genetic difference between Japanese living in the north and south, this finding suggests that an exogenous agent may play a role in the induction of the disease. A report from Hawaii that could not document a case of Behcet disease in the Nisei population is of interest as well [*Hirohata T. et al., 1975*]. This observation also supports the concept that an exogenous factor found in different parts of Japan might play a role in development of the disease. Although several familial cases [*Dundar S. et al., 1985; Villanueva J. et al., 1993*] and a pair of monozygotic brothers [*Hamuryudan V. et al., 1991*] concordant for the syndrome have been reported, no consistent inheritance pattern has been noted [*Stewart B., 1986; Mizuki N. et al., 1992*].

Behcet disease is a multisystem inflammatory illness characterized by intraocular inflammation, oral and genital ulcerations, skin lesions (erythema nodosum-like lesions, acneiform lesions or folliculitis, thrombophlebitis, cutaneous hypersensitivity) and a variety of other disorders involving multiple organ systems in the body (the joints, the intestine, epididymis, vascular system, and the central nervous system). Behcet disease is characterized by recurrent episodes of inflammation involving one or more organ systems. The onset of these episodes is generally sudden. Inflammation then subsides over a period of several weeks.

Non-ocular Disease

The most common non-ocular manifestations of Behcet disease are recurrent oral aphthous ulcers. The oral aphthous ulcers can be found not only on the gums, but also on the lips, posterior pharynx, uvula, hard palate, and tongue. The ulcers are painful, round or oval and usually small and sharply defined. They ordinarily heal in 7 to 10 days. Scarring occurs only with particularly large ulcers.

A variety of skin lesions can occur in patients with Behcet disease. Erythema nodosum-like lesions are noted frequently on the anterior surface of the legs, but they can also be seen on various body surfaces including the face, neck, and buttocks. The lesions are slightly raised, tender red nodules. They involute after several weeks without ulceration. Acneiform lesions or folliculitis are common on the backs and faces of the patients. Because corticosteroid therapy can induce similar skin lesions, acneiform lesions in patients receiving corticosteroids have no diagnostic meaning. Thrombophlebitis is less common than the former two skin lesions. It usually occurs in the extremities and can be migratory. It can also develop after an injection or following venipuncture for blood sampling.

"Cutaneous hypersensitivity" is a characteristic feature of Behcet disease. A clinical manifestation of cutaneous hypersensitivity in male patients is hyperreaction of the skin after shaving. Cutaneous hypersensitivity can be tested with the "prick" test, in which a pustule forms after scratching the skin with a needle.

Genital ulcers in male patients may appear on the scrotum and penis and therefore easily identified. In female patients lesions can develop on the vulva or the vaginal mucosae. The genital ulcers can be deep and can leave scars. An examination of the genital region can therefore be useful if a suspected Behcet disease may be present.

At least half of Behcet disease patients are affected by a nonmigratory and nondestructive arthritis. The most commonly affected joint was the knee.

Vessels of all sizes can be affected in Behcet disease. The patients who develop vasoocclusive inflammatory changes in large vessels, with aneurysm or thrombus formation, are considered to have the "vasculo-Behcet" "angio-Behcet", or "cardio-Behcet" disease variant. Each of these variants has a poor prognosis, because infarction or rupture of an aneurysm can be life threatening.

Involvement of the central nervous system is seen in 8% to 10% of Japanese with Behcet disease; a predominance of male patients is observed [*Inaba G., 1989]*. In 68 autopsy cases studied by G. Inaba, multiple lesions in the central nervous system were found, particularly in the thalamus, basal ganglia, and the brainstem.

In addition to a variety of neurologic findings such as cranial nerve palsies and pyramidal and extrapyramidal signs, psychiatric disorders may appear. Behcet disease has also been implicated as a cause of vertigo, hearing loss; these changes are believed to have a vasculitic cause.

Examination of the cerebrospinal fluid during the acute stage of neuro-Behcet disease discloses a pleocytosis with neutrophils as the predominant cellular component.

Ocular disease

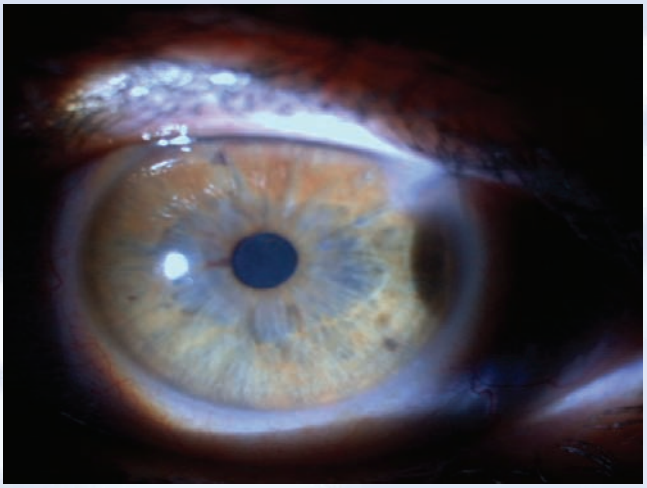
The ocular manifestations of Behcet disease have serious implications for patients. Visual prognosis, particularly for patients having inflammation of the posterior segment, is poor. An analysis of long-term visual acuity outcomes disclosed that a good visual acuity (>20/40 was retained for almost 10 years in all the eyes that had anterior uveitis alone, whereas only one quarter of the eyes with posterior involvement retained good visual acuity 5 years after the onset of uveitis [*Mishima S. et al., 1979*].

Although the disease can affect the anterior and posterior portions of the eye separately, the majority of patients have panuveitis or posterior uveitis; only a small portion (10%) of patients has only anterior uveitis. Ocular disease usually develops 2 to 3 years after the initial lesions of Behcet disease, which in most patients are oral aphthous ulcerations. However, ocular disease is the initial manifestation of Behcet disease in about 20 % of cases [*Imai Y., 1971*]. The disease is almost always bilateral; only rarely does uveitis develop in a single eye. A long-term study in Japan found that 93.6% of patients have bilateral disease, but in some cases, the interval between involvement of the two eyes was more than 5 years [*Imai Y., 1971*].

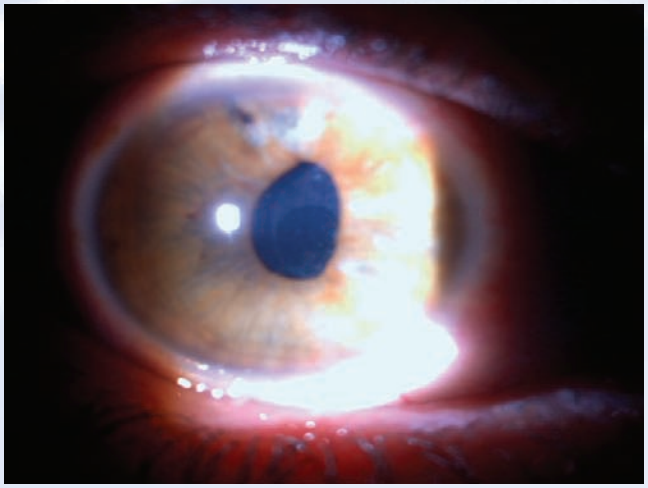
Behcet disease is characterized by explosive attacks of intraocular inflammation. These episodes resolve spontaneously over several weeks with or without treatment. Patients can have many recurrent episodes of uveitis, which result in irreversible damage to intraocular tissues. Anterior uveitis is characterized by gross hypopyon formation in about one third of cases [*Mishima S. et al., 1979*]. The hypophon is composed primarily of neutrophils [*Shimada K. et al., 1972*]. In eyes with severe iridocyclitis in which no hypopyon is seen by direct examination with the slit lamp biomicroscope, a small layering of leukocytes can be observed in the angle by gonioscopy ("angle hypopyon"). The iridocyclitis is nongranulematous in nature, and cells move freely in the currents of the aqueous humor. A characteristic feature of the hypopyon of Behcet disease is that it shifts with gravity as the patient changes head positions. The hypopyon resolves spontaneously after several days, without sequelae. Posterior synechiae, iris atrophy, and peripheral anterior synechiae may develop during the course of repeated ocular inflammatory attacks. Peripheral anterior synechiae or iris bombe from pupillary seclusion may cause secondary glaucoma. An isolated vitreous inflammatory reaction is not characteristic of Bahcet disease.

Retinal Disease: Retinal disease is the most serious complication of Behcet disease. The funduscopic examination reveals venous engorgement, retinal hemorrhages, yellow-white exudates, retinal infiltrates, intense retinal oedema, and hyperemia and edema of the optic disc. Retinal infiltrates have been reported as pathognomonic findings [*Graham E. et al., 1989*]. There is an accompanying vitreous inflammatory response. Retinal vasculitis is very intractable to treatment and rarely disappears completely. Patients with chronic posterior uveitis and retinal vasculitis may have anterior uveitis attacks with variable frequency; often the periods of remission in their anterior uveitis are longer in the late stages of the disease, possibly because of intense medications directed to the posterior disease.

At the very late stages the fulminant picture of active retinal disease, with intraretinal oedema, hemorrhage, infiltrates, and venous engorgement, is replaced with an atrophic retina and optic disc, sheathed arteries and veins, and a variable degree of chorioretinal scars and retinal pigment epithelial alterations with a trace to mild vitreous inflammation. Retinal neovascularization results in retinal or vitreous hemorrhage and is occasionally observed. Neovascular glaucoma occurs in as many as 6% of patients and often results in *phthisis bulbi*.



Picture 1. *The peripupilar atrophy of iris.*



Picture 1a. *Behcet disease without peripupilar atrophy of iris.*

MATERIAL AND METHODS

A retrospective review of 56 patients (age range: 16-54) with ocular Behcet disease from different regions of Armenia seen at the Uveitis Department of S.V. Malayan Ophthalmologic Center in a period of 2002-2007 was performed.

RESULTS

The Behcet disease constituted 11.2% of all uveitis referral patients. The median age at onset was 34 years. Male/female ratio was 3.6:1. The active disease was observed in all patients. The mean follow-up period was 3 years. The pathologic changes of fundus (cystoid macular oedema, optic nerve oedema and atrophy, retinal hemorrhages, retinal occlusive vasculitis and retinal infiltrates) were present in 95% of patients. After the initiation of treatment mentioned changes were observed only in 25% of patients.

Table 1.

The frequency of pathologic changes of fundus at the first visit and after initiation of treatment

Pathologic changes	First visit	Last visit
Cystoid macular oedema	41.7%	8.4%
Snowballs	29.2%	12.5%
Occlusive vasculitis	4.2%	4.2%
Retinal hemorrhages	29.2%	16.7%
Retinal infiltrates	16.7%	9.5%
Optic nerve atrophy	16.2%	16.2%

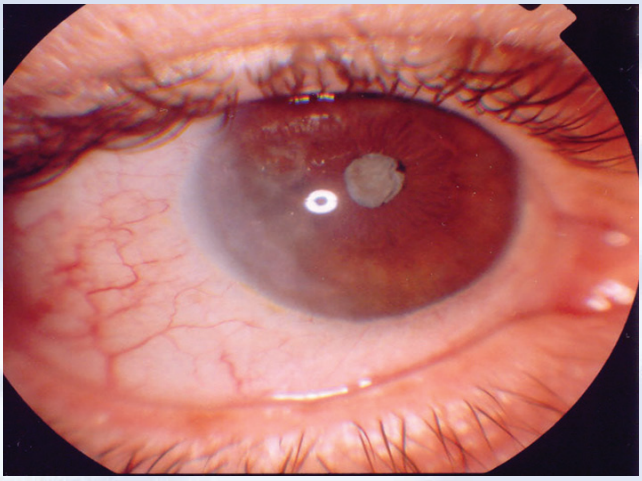
Our study revealed no significant difference of disease frequency between the regions of Armenia.

Cyclosporine (Sandimune, Neoral) was the most effective medication for the management of disease though the majority of our patients received a combination of Imuran (Azathioprine) (1.5-2.0 *mg/kg/day*) and Colchicine (1.0 *mg/kg/day*) associated with subtenon injection of Diprospan 1.0 (*N* 10), which are much affordable and only 2 patients received Cyclosporine.

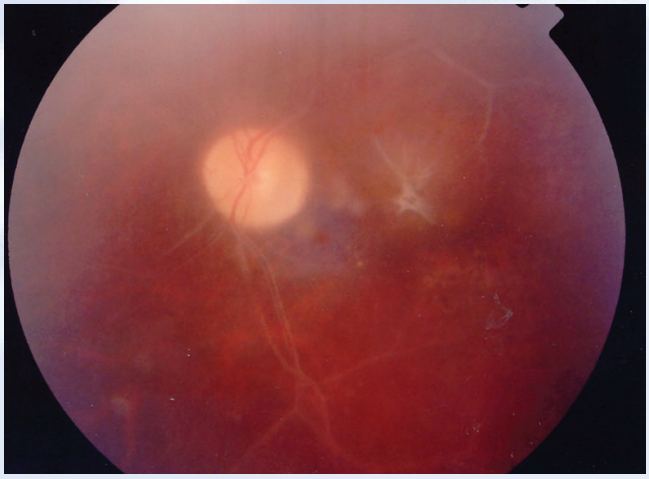
Table 2.

The frequency of Behcet disease

Cities/regions	Number of patients	Percentage (%)
Yerevan	15	26.79%
Giumry	5	8.93%
Hrazdan	4	7.14%
Artashat	4	7.14%
Sevan	5	8.93%
Vanadzor	3	5.36%
Akhtala	3	5.36%
Gavar	4	7.14%
Ashtarak	3	5.36%
Etchmiadzin	3	5.36%
Talin	4	7.14%
Artik	3	5.36%
Akhltskha	2	3.57%
Artsakh	2	3.57%



Picture 2. *Associated interstitial keratitis.*



Picture 2a. *Occlusive vasculitis.*

Two of 46 patients had atypical clinical presentation at the first visit. One of the patients had associated Fuchs' like anterior picture. Pictures 1-1a reflect the peripupilar atrophy of iris which is characteristic for Fuchs' uveitis syndrome or otherwise Fuchs' heterochromic iridocyclitis.

Fuchs' uveitis syndrome has been described in association with ocular toxoplasmosis, sarcoidosis, *retinitis pigmentosa*, but has never been described with Behcet disease. The other patient had associated interstitial keratitis at presentation which responded to steroid treatment (Pictures 2-2a). This is also an interesting observation which, to our knowledge, has never been described as well.

DISCUSSION

Our study revealed the disease to be much common in our clinic. There was no significant difference of disease frequency between the regions of Armenia, taking into consideration the number of population of different regions. Cyclosporine was the most effective medication for the management of disease though our patients are mainly receiving Imuran (1.5-2.*5 mg/kg/day*) and Colchicine combination associated with subtenon injection of Diprospan 1.0 (*N* 10), which is affordable as well as effective. The significant point of our study was the association of Behcet disease with Fuchs' uveitis syndrome which was atypical clinical presentation and has never been reported. ■

REFERENCES

1. *Behcet H.* Uber die rezideivierende, aphthose, durch ein Virus verursachte Geschwure am Mund, am Auge und an den Genitalen. Dermatol. Wochenschr. 1937; 46: 414-419.
2. *Dundar S.V., Gencalp U., Simsek H.* Familial cases of Behcet disease. . Br. J. Dermatol. 1985; 113: 319-321.
3. *Graham E.M., Stanford M.R., Sanders M.D. et al.* A point prevalence study of 150 patients with idiopathic retinal vasculitis. I. Diagnostic value of ophthalmologocal features. Br. J. Ophthalmol. 1989; 73: 714-721.
4. *Hamuryudan V., Yurdakul S., Ozbakir F. et al.* Monozygotic twins concordant for Behcet syndrome. Arthritis Rheum. 1991; 34:1071-1072.
5. *Hirohata T., Kuratsume M., Nomura A.* Prevalence of Behcet syndrome in Hawaii, Hawaii Med. J. 1975; 34: 244-246.
6. *Imai Y.* Studies on prognosis and symptoms of Behcet disease. Jpn J. Clin. Ophthalmol. 1971; 25: 661-694.
7. *Inaba G.* Behcet disease. In: McKendall R.R., editor. Handbook of clinical neurology. Vol 6. Viral disease. Amsterdam. Elseivier. 1989. P. 593-610.
8. *Mishima S., Masuda K., Izawa Y. et al.* Behcet disease in Japan: Ophthalmologic aspects. Trans. Am. Ophthalmol. Soc. 1979; 77: 255-279.
9. *Mizuki N., Ohno S., Tanaka H. et al.* Association of HLA B-51 and lack of association of class II alleles with Behcet disease. Tissue Antigens.. 1992; 40: 22-30.
10. *Shimada K., Yaoita H, Shikano S.* Chemotactic activity in the aqueous humor in patients with Behcet disease. Jpn J. Ophthalmol. 1972; 16: 84-92.
11. *Shimizu T., Ehrlich G.E., Ihaba G.* Behcet disease (Behcet syndrome). Semin. Arthritis. Rheum S. 1979. P.223-260.
12. *Stewart B.* Genetic analysis of families of patients with Behcet syndrome: data incompatible with autosomal recessive inheritance. Ann. Rheum. Dis. 1986; 45: 265-268.
13. *Villanueva J.L, Gonzalez- Dominguez J., Gonzale-Fernandez R. et al.* HLA antigen familial study in complete Behcet syndrome affecting three sisters. Ann. Rheum. Dis. 1993; 52: 155-157.
14. *Yazici H.* Behcet syndrome. In: Klippel J.H., Dieppe P.A., editors. Rheumatology. London. Mosby. 1994. 6. 20. 1- 6. 20. 6.
15. *Yazici H., Tuzun Y., Pazarli H. et al.* Influence of age of onset and patient's sex on the prevalence and severity of Behcet syndrome. Ann. Rheum. Dis. 1984; 43: 783-789.
16. *Yurdakul S., Gunaydin I., Tuzun Y. et al.* The prevalence of Behcet syndrome in a rural area in Northern Turkey. J. Rheumatol. 1988; 15: 820-822.