

# Treatment and visual prognosis in Behçet's disease

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**SUMMARY** For the last decade we have observed and regularly followed 49 patients with the ocular type of Behçet's disease. Thirty-six patients were males and 13 were females. Regardless of whether the initial ocular presenting symptoms were in the anterior or posterior segment, both segments were involved within two years. Sterile hypopyon was recorded in 17 out of the 49 patients during the process of follow-up. In three of the patients hypopyon was the presenting symptom. Characteristically there was a lack of corneal or scleral involvement in the disease process. All patients responded initially to treatment with steroids, but 42 had a course of treatment with cytotoxic-immunosuppressive drugs for various lengths of time after 'resistance' to steroids developed. Although definitely effective in reducing the intensity of the ocular inflammatory processes, it is not clear yet whether these modes of treatment have any dramatic effect of the visual prognosis of the affected eyes. Despite intensive follow-up and treatment, loss of useful visual acuity has occurred in 74% of the eyes six to 10 years after the start of the ocular symptoms.

Probably identified already by Hippocrates<sup>1</sup> and clinically described in a few reports early this century,<sup>2,5</sup> Behçet's disease was recognised as a clinical entity only in 1937.<sup>6</sup> Though originally described as a disease manifested by aphthous stomatitis, genital ulcers, and visual disturbances (the classical triad), it soon became evident that Behçet's disease is not confined only to the above organs.<sup>7,9</sup> Because of the multisystemic manifestations, confusion over the criteria for diagnosis and the incidence of involvement of the various organs had developed. Thus the incidence of ocular manifestations varies from 23% to 96% of cases whether the report originated from a dermatology<sup>10</sup> or ophthalmology<sup>11</sup> department. Aware of these possible biases, we have been classifying Behçet's disease as ocular type when the classical triad of symptoms is observed and non-ocular type if the diagnostic criteria as suggested by the Behçet's Syndrome Research Committee of Japan are met<sup>12</sup> but the eyes are not involved. We report herein our observations on the treatment and visual prognosis of the ocular type of Behçet's disease during the last decade.

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## Materials and methods

### PATIENTS

During the decade 1975-85, 70 patients with the diagnosis of Behçet's disease were examined in our clinic. Twenty-one patients did not meet the criteria for the ocular type of Behçet's disease. Forty-nine had aphthous stomatitis, ulcers of the genitalia, and ocular inflammation and were classified as suffering from the ocular type of Behçet's disease. All have been followed up regularly with at least three follow-up visits per year.

### TREATMENT

Corticosteroid drops (dexamethasone 0.1%, prednisolone 1.0%, fluometholone 0.1%) were instilled four to eight times daily according to the severity of the ocular reaction and mydriatics-cycloplegics (atropine 1%, scopolamine 0.25%, neosynephrine 10%, cyclopentolate 1%) if the anterior segment was affected. Subconjunctival or subtenon slow-release steroid preparations (Depo-Medrol (methylprednisolone acetate) 20 mg) were injected if the initial response to drops was not satisfactory. Systemic treatment was started only if the patient presented with marked posterior segment involve-

ment and/or prominent anterior segment inflammatory activity that did not respond to local therapy in one or both eyes. Initially all patients were treated with steroids, receiving oral prednisone 1 to 2 mg/kg/day for four days, with a gradual decrease of the dose in accordance with the clinical signs. When the ocular inflammatory reactions were not controlled by a dose less than 35 mg/day (approximately 0.5 mg/kg/day) and exacerbations were observed under this regimen, the steroids were gradually stopped and the patients treated with the second line of drugs.

As second line the patients received during this period any of the following: colchicine (18 patients) with an initial dose of 0.05 mg/kg/day and gradual reduction to a maintenance dose of 0.5 mg daily within one month; chlorambucil (20 patients) in doses of 0.1 to 0.2 mg/kg/day as a starting dose, titration according to the inflammatory and haematological response, and a final maintenance dose of 2 mg/day; azathioprine (four patients) in doses of 2 mg/kg/day and a maintenance dose of 75 to 100 mg/day. Two of the patients treated with chlorambucil underwent plasmapheresis because of frequent relapses. Two of the patients treated initially with colchicine were later tried on levamisole 50 mg orally thrice daily.

## Results

Of the 49 patients with the ocular type of Behçet's disease 42 were born in countries of the Mediterranean basin, five in Iran, and two in Iraq (Table 1). Of the 12 patients born in Israel the parents' origin was in countries of the Mediterranean basin in 10 cases, from Russia in one case, and from Poland in one case. Thirty-six patients were male (73%) and 13 were female (27%).

The ophthalmic manifestations observed in the 49 patients encompassed both the anterior and posterior

segments and reflected the vasculitis of the ocular blood vessels. Careful examination of the peripheral fundus disclosed choroidal and/or retinal exudates, with sheathing of the blood vessels in all cases. In three of the cases the findings in the peripheral fundus were the earlier ocular manifestations with anterior uveitic signs appearing at a later stage of the disease. Hypopyon was recorded in 17 out of the 49 patients at different stages and was observed more than once in seven cases. In 13 patients hypopyon was a late phenomenon appearing during exacerbation periods. In four eyes of four patients hypopyon was an early event. In three of these patients hypopyon was the presenting ocular manifestation leading to the diagnosis of Behçet's disease. None of our patients showed any involvement of the cornea and/or sclera during the period of follow-up.

All patients initially responded favourably to high doses of corticosteroids with a marked decrease in ocular inflammatory signs and improvement of visual acuity. However, most of the patients had relapses and exacerbations of the inflammatory signs on lowering of the daily steroid dose. Forty-two of the patients were subsequently treated with chlorambucil (20 patients), colchicine (18 patients), and azathioprine (four patients), while seven patients continued to be treated with high doses of steroids. As illustrated in Table 2, all seven patients under maintained high doses of steroids responded to the treatment and had a remission period ranging from three to 14 months with an average of eight months. Treatment with chlorambucil induced remission of the ocular inflammatory processes in 16 out of 20 patients. In four patients no benefit was observed. While the average period of remission for the whole

Table 1 Countries of birth of patients with the ocular type of Behçet's disease

Country	Number of patients
Jordan	16
Israel	12*
North Africa	11
Iran	5
Greece	2
Iraq	2
Turkey	1
Total	49

\* Of the 12 patients born in Israel the parents of 10 originated from countries of the Mediterranean basin. In one case the parents originated from Russia and the other from Poland.

Table 2 Modes of treatment\* modalities for the 49 patients

Treatment	Number of patients		Period of remission (months)	
	Total	Responders	Average	Range
Steroids	7	7	8	3-14
Chlorambucil	20	16	6	0-25
Colchicine	18	8	3	0-7
Azathioprine	4	1	2	0-8
Plasmapheresis†	2	1	2	0-4
Levamisole‡	2	1	2	0-4

\* All patients were initially treated with steroids and switched to another treatment after resistance to steroids developed. The seven cases that remained under steroids received increased doses and were not given a trial of immunosuppressive drugs because of secondary considerations.

† Two of the patients who were treated with chlorambucil and relapsed subsequently underwent plasmapheresis.

‡ Two of the patients who were treated with colchicine and relapsed were treated with levamisole.

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group treated with chlorambucil was approximately six months, two of the responding patients had no relapses for 24 and 25 months in each case. The response to colchicine or azathioprine was less obvious. Eight of 18 patients responded favourably to colchicine with a relatively short period without exacerbations, while only one patient out of four treated with azathioprine showed a significant decrease of the inflammatory signs. After failure of the cytotoxic immunosuppressive drugs, patients were again treated with high doses of steroids, with variable degree of responses. Two patients also underwent plasmapheresis and two were treated with levamisole without success (Table 2).

Secondary complications were observed in almost all eyes. These included early events such as lenticular changes, posterior synechiae, secondary glaucoma, vitreous opacities and organisation, and macular oedema. Later complications included iris and retinal neovascularisation, traction retinal detachment, vascular insufficiency, and optic atrophy. While the early secondary complications were relatively amenable to treatment and/or control, the late complications were uncontrollable and were the cause of the poor vision or intractable blindness.

Table 3 illustrates the deterioration in visual acuity that occurred during the period of follow-up. Of the 49 patients (98 eyes) observed during three years or less after initiation of the ocular manifestations 51 retained excellent visual acuity and only two eyes showed total loss of vision. Thirty-nine patients (78 eyes) were followed for up to six years. Of these, 25% had finger counting at a distance of 1 metre to distinction of hand movements in front of their eyes or lost vision totally. Among the 26 patients (52 eyes) followed for up to 10 years five eyes retained a good visual acuity of 6/6 to 6/12, while 30% of the eyes lost vision totally, 26% had only finger counting to hand

movements, and an additional 18% had visual acuity within the range of legal blindness.

**Discussion**

Deeper knowledge of the possible affection of various organs and the emergence of complex diagnostic criteria with subtype divisions to 'complete,' 'incomplete,'<sup>12</sup> and even 'suspected' types of Behçet's disease led to disparate reports on the incidence of involvement of the various organs in this disease.<sup>10-15</sup> It appears that these large discrepancies along with the optimistic or pessimistic outcome of the various modes of treatment have largely depended on the specialty of the reporter(s) and his subjective evaluations, biased in most cases by insufficient follow-up data.<sup>16-18</sup> Although Behçet's is undoubtedly a multisystem disease, the ocular inflammatory signs and the high incidence of loss of visual acuity are its most dramatic effects. Because on the one hand of the prominence of the ocular manifestations and on the other our earlier clinical impressions of the possible difficulty of differential diagnosis from other collagen disease in the absence of ocular involvement, it has been our practice during the last decade to divide Behçet's disease into 'ocular' and 'non-ocular' types. Based on similar observations, a subdivision into mucocutaneous and neuro-ocular types of Behçet's has been suggested.<sup>19</sup> Forty-nine patients fulfilled the criteria for the ocular type of Behçet's disease and were followed up regularly for up to 10 years in our clinic. This unique group enabled us to assess the rate of visual deterioration in this disease. We have observed that only 2% of the eyes lost total vision within the first three years after initiation of the ocular symptoms, while within 10 years 30% lost vision totally, 26% remained with finger counting or perception of hand movements in front of their eyes, and an additional 18% were within visual acuity of legal blindness. Therefore in our group of patients, regardless of the type of treatment, 74% of the eyes lost useful vision six to 10 years after initial diagnosis.

The ophthalmic manifestations of Behçet's disease are the reflection of the uveitis and retinal vasculitis. These manifestations involve both the anterior and posterior segments within two years of the recording of initial symptoms regardless of whether the initial symptoms were an iridocyclitis with or without hypopyon or a vasculitis of the vessels in the fundus periphery. Apart from the recurrent sterile hypopyon (when present) and the pipe stem sheathing of the retinal blood vessels at a later stage of the disease, no other ocular affections or secondary complications are specific to Behçet's disease. However, in our opinion the lack of corneal or scleral

Table 3 Residual visual acuity during follow-up

Visual acuity	Years of follow-up					
	≤3		>3-6		>6-10	
	No. *	%	No.	%	No.	%
6/6-6/12	51	52	22	28	5	10
6/15-6/30	30	31	20	26	8	16
6/60-6/120	9	9	13	17	9	18
FC-HM	6	6	18	23	14	26
NLP	2	2	5	6	16	30
Total	98	100	78	100	52	100

\* No. = Number of eyes in each group, with % of total.  
 FC = finger counting at a distance of 1 to 3 m.  
 HM = perception of hand movements.  
 NLP = no light perception (generally these eyes were phthisic).

involvement is characteristic. Therefore, when keratitis and/or episcleritis are observed, as in some reports,<sup>20</sup> possible secondary phenomena and/or a differential diagnosis from other collagen diseases has to be considered.

Reliable figures regarding the natural history of visual deterioration in Behçet's disease are not available, while the prognostic effect of the various modes of treatment on the visual outcome is not clear. It is our clinical impression that the frequency of the attacks of ocular inflammatory exacerbation and their length are diminished by treatment with large doses of corticosteroids and/or immunosuppressive drugs. However, as observed during this study, the long-term prognosis for vision remains very poor. High doses of steroids can control the inflammatory processes and a unanimous response to the steroids is observed initially. However, a state of resistance to the steroid treatment develops, followed by an increase in the severity and number of exacerbations. The effect of cytotoxic-immunosuppressive drugs on the ocular manifestations of Behçet's disease has been variable. Chlorambucil was clearly beneficial in 75% of the patients. Colchicine was less effective and reduced temporarily the ocular inflammatory signs in only 45% of the cases, while the response to azathioprine was negligible. Although only 16 out of 20 patients responded favourably to treatment with chlorambucil, two of these were in remission for 24 and 25 months, the longest period without inflammatory activity we have observed so far in Behçet's disease. These results, although not fully compatible with the outstanding benefits reported by others using chlorambucil,<sup>21,22</sup> may explain the enthusiasm for this drug. It is undeniable that both the large doses of steroids and to a greater extent the long-term use of chlorambucil are not without harm and may have deleterious outcomes.<sup>20,23,24</sup> These have to be considered against the threat of blindness when deciding about the type of treatment in Behçet's disease.

Recently the influence of cyclosporin A (CsA) on the acute exacerbations of Behçet's disease has been tested with some encouraging results.<sup>25-27</sup> However, owing to the chronicity of the disease process and the unpredictability of remissions and exacerbations of the inflammatory reactions, there is a need for masked evaluations, longer follow-up data, and larger numbers of patients for adequate and unbiased testing of this novel drug. Such studies are now in progress and will hopefully provide the needed information in the future.

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