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Behcet's Disease- Comparing Three Decades of Treatment Response at the National Eye Institute

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Abstract

Background—The goal of the present study was to analyze differences in response to treatment of ocular Behcet's disease (BD) in the 1960's, 1980's and 1990's.

Methods—Medical records of 120 patients with uveitis due to BD followed at the National Eye Institute (NEI), National Institutes of Health, from 1962 to 2004 were reviewed.

Results—All the patients were categorized in 3 groups according to the time of follow-up: first group was followed from 1962 until 1972, second group from 1983 until 1992 and the third group from 1992 through 2004. Snellen visual acuity was converted to logMAR values. The range of values for inflammation was 0.5 (trace), 1 (mild), 2 (moderate) and 3 (severe). There were 45 patients (89 affected eyes) in the 1960's group, 26 patients (52 eyes) in the 1980's group and 49 patients (94 eyes) in the most recent group. Statistical analysis showed that the mean logMAR score decreased with each decade. Mean visual acuity in the 1990's group was significantly better than in the previous decades ($p < 0.001$ for the 1960's group and $p = 0.019$ for the 1980's). The mean inflammation score was significantly higher in the 1960's than in the subsequent decades ($p < 0.001$ both for 1980's and for the 1990's).

Interpretation—BD is a severe blinding disorder. There was a definitive trend toward improvement in clinical outcome from the 1960's to 1990's. We attribute this trend to the introduction of newer, more potent corticosteroid-sparing agents and targeted therapy.

Introduction

Behcet's disease (BD) is a chronic, multisystem inflammatory disorder, characterized by relapsing oral aphthous and genital ulcers, ocular inflammation, erythema nodosum and folliculitis-like lesions of the skin, arthritis, and central nervous system involvement. The disease described initially by Hippocrates (460–377 BC)¹ was rediscovered by two physicians who published their findings in 1931² and 1937³ respectively.

Necrotizing and obliterative vasculitis affects both the arteries and veins in all organ systems.⁴ Ocular involvement in BD is about 70 % of cases.⁴ The typical course of the ocular disease is relapsing remitting uveitis, most commonly panuveitis. Purely anterior involvement is less common, and it includes: iridocyclitis with or without hypopyon, conjunctivitis, conjunctival ulcers, keratitis, episcleritis and scleritis.^{5,6} Posterior involvement may include vitritis,

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vitreous hemorrhage, retinal vasculitis, retinal vein occlusion, retinal neovascularization, cystoid macular edema and optic neuritis.^{7,8}

In the present study we retrospectively analyzed demographic and clinical features, complications and visual outcomes of 120 patients with ocular BD followed at the National Eye Institute, National Institutes of Health, Bethesda, Maryland. Our goal was to compare the clinical parameters and treatment of uveitis in an attempt to elucidate an improvement in mean visual acuity and inflammation score over the last several decades.

Methods

The clinical records of patients seen in the Ocular Immunology and Uveitis Clinic at the National Eye Institute, under IRB approved protocols, from 1960 to 2004 were reviewed under protocols approved by the institutional review board, and patients with the diagnosis of BD were identified. A total of 148 patients met the International Study Group for Behçet's Disease criteria.⁶ Twenty eight patients (18.9%) did not have any ocular manifestations of the disease, and they were excluded from the study. For 120 patients (81.1% of all BD patients) the diagnosis was uveitis. They were divided in 3 groups according to the time of follow-up: the first group was followed from 1962 until 1972 (1960's group), the second group from 1983 until 1992 (1980's group) and the third group from 1992 through 2004 (1990's group).

Data on age, sex, ethnicity, time of the diagnosis, laterality, type of uveitis (anterior, posterior, or panuveitis), ocular and extraocular manifestations of the disease, ocular complications, anti-inflammatory and immunomodulatory therapy and follow-up were collected. Patients who experienced only attacks of iridocyclitis were defined as patients with anterior uveitis; patients who developed retinitis, retinal vasculitis with or without papillitis in the absence of iridocyclitis have been classified as patients with posterior uveitis; and those patients who had both anterior and posterior uveitis were classified as having panuveitis. Retinal vasculitis was defined as perivascular sheathing by indirect ophthalmoscopy and evidence of perivascular leakage and vascular occlusion on fluorescein angiogram. Macular edema was defined as thickening of macula on stereoscopic ophthalmoscopic examination and (or) leakage of macula on fluorescein angiogram. Scarring, atrophy and infarct of macula were defined as maculopathy.

Visual acuities and degrees of inflammation of each patient at each visit were recorded. Snellen visual acuity was converted to a logMAR value. Visual acuities collected at each visit throughout the years of follow-up were grouped according to the decade of follow-up and mean visual acuities were calculated for each decade. The range of values for inflammation in the anterior chamber and vitreous was 0.5 (trace), 1 (mild), 2 (moderate) and 3 (severe). Since measurements on eyes were repeated over time and eyes were nested within a patient, a linear model with mixed fixed effect (decade) and random effects (patient and eye) was employed to test differences in the mean of the visual acuity and logMAR outcomes. Since follow-up varied among patients and between decades, the model also included a term to adjust for follow-up differences. All other outcome variables were yes/no attributes, and these were analyzed as comparisons of percent of patients among decades. If an ocular attribute was present in at least one eye, then the attribute was deemed present in the patient for the purpose of person-wise analyses. All percent comparisons were made by Fisher's exact test at the 0.05 level of significance.

Results

There were 45 patients (89 affected eyes) in the 1960's group, 26 patients (52 eyes) in the 1980's group and 49 patients (94 eyes) in the most recent group. Race and sex distribution is

reflected in Table 1. Caucasians were a predominant group in all 3 decades, and there were more men than women. The disease was bilateral in 115 patients (96 %). One hundred fourteen patients (95%) were classified as having panuveitis, 5 patients (4 %) with anterior uveitis, and 1 patient with posterior uveitis. Median age at diagnosis was 28 years for all patients. (Table 1). Median follow-up in the 1960's group was 0.5 years, in the 1980's - 2.9 years and in the most recent group- 1.8 years (Table 1). Mean time between the diagnosis of BD and presentation to NEI was 3.8 years in the 1960's group, 3.4 years in the 1980's group and 4.0 years in the most recent group.

Extraocular manifestations are shown in Table 2. All of the patients had recurrent oral ulcers. Genital ulcers were the second most common sign (69% of the total), followed by skin lesions (58%), arthritis (38%), central nervous system manifestations (16%), vascular lesions (5%) and epididymitis (4%). There was no statistical difference found between decades.

The ocular complications observed are listed in Table 3. Cataract was the most common complication developing in 38% of patients, followed by cystoid macular edema (32%). All retinal detachments were associated with retinal tears and were rhegmatogenous in nature; they complicated the course in 6% of patients. Comparing changes between decades, we found that there was a statistically significant drop in the rate of papillitis from 1960's compared to 1990's ($p=0.001$) and from 1980's compared to 1990's ($p=0.002$). There was also a statistically significant reduction of intra- and subretinal hemorrhage from the 1960s to the 1990s ($p=0.035$). Analysis of visual acuities showed that the mean logMAR score decreased with each decade (Table 4). Mean visual acuity in the 1990's group was significantly better than in the previous decades ($p<0.001$ for the 1960's group and $p=0.019$ for the 1980's). The mean inflammation score was significantly higher in the 1960's than in the subsequent decades ($p<0.001$ both for 1980's and for the 1990's) (Table 4).

Table 5 summarizes medications used in the treatment of BD since 1962 through 2004 at the National Eye Institute. Ninety six percent of patients with ocular BD were treated with systemic steroids in the 1960's group; 69% of all patients in that group had been treated with systemic steroids as monotherapy. In the 1980's group all the patients received systemic corticosteroids at some point, but only 2 patients (8%) had been treated with steroids as monotherapy. Eighty nine percent of patients in this group had been on long-term cyclosporine therapy, chlorambucil has been used in 15%, cyclophosphamide in 12%, and azathioprine in 8%. In 1990's group 84% of patients have been treated with systemic steroids, 16% of patients in this group having been treated with steroids as monotherapy. Cyclosporine was used in 55% of patients in the 1990's group, daclizumab in 31%, mycophenolate mofetil in 16%, infliximab in 14% and sirolimus in 2%. The use of steroids as monotherapy fell significantly from 1960's (69%) compared to 1980's (8%) and 1990's (16%) ($p<0.001$).

Interpretation

BD may have devastating ocular consequences. It has been reported that vision was lost in an average of 3.36 years after the onset of visual symptoms.⁷ Approximately 12% of acquired vision loss in adulthood in Japan was caused by BD.⁸ In a study from Israel loss of useful visual acuity occurred in as many as 74% of the eyes during the first 6 to 10 years after the onset of the ocular symptoms.⁹ A recent study from Turkey analyzing outcomes in 880 patients estimated that the risks of losing useful vision for males and females were 21% and 10% at 5 years and 30% and 17% at 10 years.¹⁰ Reports have recently emerged from Japan stating that there was an overall tendency for a milder disease.¹¹⁻¹⁴ The authors noticed that the number of ocular attacks had decreased in the 1990's compared to 1980's, the percentage of patients taking cyclosporine and cyclophosphamide had decreased and visual outcomes had improved.¹⁴ However, the same study did not find any significant difference in the rate of complications

over time or in the rate of systemic manifestations of the disease. There was no change in the anatomic location, laterality of the disease or predominance of male sex. It was also noticed that the time between the first symptoms of the ocular disease and presentation to the uveitis specialists has decreased in the more recent group of patients. This was attributed to a higher education of patients and growing awareness of the disease.¹⁴ The Turkish study also noticed improved visual outcomes in patients who presented after 1990, but the authors have attributed this to more aggressive treatment approach and availability of cyclosporine A.¹⁰ It is believed that newer immunomodulating and biologic agents may offer an improved prognosis in patients with BD.¹⁰

Our data showed that Caucasians were a predominant group in all three decades at our institution. Males had a slight predominance over females. Other published studies reported a significant male predominance.^{10,15–17} We did not compare the severity of ocular involvement or differences in complications between males and females as this was not the goal of this study. Different studies have reported that women have a milder course of the disease and men have more visual complications and visual loss.^{10,13,18,19} The disease was bilateral in the majority of patients (96 %) in the current study. This corresponded to the data of many reports on high frequency of bilateral involvement^{8,11,15–19}. Ninety five percent of our patients were classified as having panuveitis. Other published studies also indicate the propensity for posterior involvement in ocular BD.^{8,15–17} Median age at diagnosis was 28 years for all patients in our study. The average age of onset of ocular BD was between 25 and 35 years old in other studies.^{10,14,17,20–22}

All of the patients in our study had recurrent oral ulcers. Genital ulcers were the second most common sign (69%), followed by skin lesions (58%), arthritis (38%), central nervous system manifestations (16%), vascular lesions (5%) and epididymitis (4%). There was no statistical difference between decades in the frequency of extraocular manifestations of BD. This makes us speculate that the severity of the disease has not lessened over the decades.

The ocular complications observed in the current study were numerous, cataract being the most common complication, developing in 38% of all eyes, followed by cystoid macular edema (32%). There was a significant reduction of papillitis and of vitreous hemorrhage in 1990's compared to 1980's. The rate of intraretinal/subretinal hemorrhages and the frequency of branch retinal vein occlusion also have decreased significantly from 1960's to 1990's. Our study also showed that visual acuities improved with each decade. Mean visual acuity in the 1990's group was significantly better than in the previous decades. The mean inflammation score was significantly higher in the 1960's than in the subsequent decades.

While systemic steroids traditionally have been and remain the initial step in the therapy of patients with posterior uveitis and panuveitis due to BD, the approach to treatment of ocular BD has changed over time becoming more aggressive with the earlier introduction of immunomodulating agents. The treatment of ocular manifestations of BD in the early 1960's was more dependent on rheumatologist-prescribed corticosteroid therapy for extraocular manifestations of this disease, and corticosteroid monotherapy was the mainstay of treatment. This trend has changed gradually with ophthalmologists taking a lead, in recommending and administering therapy for the ocular inflammation. Cyclosporin A was a major breakthrough in the therapy of BD patients allowing long-term safe control of inflammation. In the 1990's the use of methotrexate, azathioprine and mycophenolate mofetil for posterior and panuveitis became common. The new biologic agent infliximab also became available for use. The use of steroids as monotherapy has significantly decreased over time, reflecting a trend for earlier adjunctive immunomodulatory therapy and earlier steroids withdrawal. There was a noticeable drop from 69 % percent of patients on steroid monotherapy in 1960's group to 8% and 16% in 1980's and 1990's in our study. We believe that BD remains a severe blinding disorder.

However, there was a definitive trend toward clinical improvement from the 1960's to 1990's. We attribute this trend to the introduction of newer, more potent corticosteroid-sparing agents, and the decreased use of corticosteroid monotherapy.

Acknowledgments

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Table 1

Comparison of Demographic Characteristics of Patients with Ocular Behcet's Disease and Follow-up Time.

Sex Distribution				
	60's	80's	90's	Total
Female	19 (42%)	10 (38%)	24 (49%)	53 (44%)
Male	26 (58%)	16 (62%)	25 (51%)	67 (56%)
Total	45 (38%)	26 (21%)	49 (41%)	120
Race Distribution				
	60's	80's	90's	Total
	45 patients	26 patients	49 patients	120 patients
Caucasian	35 (78%)	19 (73%)	28 (57%)	82 (68%)
African American	4 (9%)	1 (4%)	6 (12%)	11 (9%)
Hispanic	2 (4%)	2 (8%)	2 (4%)	6 (5%)
Asian	2 (4%)	1 (8%)	4 (8%)	8 (7%)
American Indian	1 (2%)	1 (4%)	3 (6%)	5 (4%)
Other/ Unknown	1 (2%)	1 (4%)	6 (12%)	8 (7%)
Age at Diagnosis (years) and Follow-up (years)				
	60's	80's	90's	Total
Median (range)	28 (13–50)	28 (15–46)	30.5 (6–59)	28 (6–59)
Missing age at diagnosis	4	3	3	10
Median follow-up (range)	0.5 (0–9.3)	2.9(0–16.8)	1.8(0–13.1)	1.7 (0–16.8)
Period between ocular onset and first visit (years)	3.8	3.4	4.0	3.8

Table 2

Comparison of Extraocular Manifestations of Behcet's Disease over Three Decades

	60's 45 patients	80's 26 patients	90's 49 patients	Total 120 patients
Oral ulcers	45 (100%)	26 (100%)	49 (100%)	120 (100%)
Genital ulcers	32 (71%)	16 (62%)	35 (71%)	83 (69%)
Skin lesions	26 (58%)	17 (65%)	27 (55%)	70 (58%)
Arthritis	13 (29%)	12 (46%)	20 (41%)	45 (38%)
Central nervous system	10 (22%)	5 (19%)	4 (8%)	19 (16%)
Vascular lesions	3 (7%)	0	3 (6%)	6 (5%)
Epididymitis	2 (4%)	1 (4%)	2 (4%)	5 (4%)

No significant difference between decades, Fisher's exact test.

Table 3

Comparison of Complications of Behcet's disease over Three Decades.

	60's 45 patients	80's 26 patients	90's 49 patients	Total (n=120) 120 patients
Cataract	19(42%)	11 (42%)	15 (31%)	45 (38%)
Macular edema	13 (29%)	9 (35%)	16 (32%)	38 (32%)
Optic atrophy	13 (29%)	8 (31%)	9 (18%)	30 (25%)
Epiretinal membrane	8 (18%)	5 (19%)	8 (16%)	21 (18%)
Glaucoma	7 (16%)	5 (19%)	6 (12%)	18 (15%)
Papillitis	13 (29%)	8 (31%)	2 (4%)	23 (19%)
Intra/subretinal hemorrhage	10 (22%)	5 (19%)	3 (6%)	18 (15%)
Intravitreal hemorrhage	5 (11%)	6 (23%)	3 (6%)	14 (12%)
Branch retinal vein occlusion	9 (20%)	3 (12%)	3 (6%)	15 (13%)
Maculopathy	5 (11%)	2 (8%)	3 (6%)	10 (8%)
Retinal detachment	2 (4%)	2 (8%)	3 (6%)	7 (6%)
Disk/retinal neovascularization	1 (2%)	3 (12%)	1 (2%)	5 (4%)
Phtisis bulbi	2 (4%)	1 (4%)	-	3 (2.5%)
Corneal ulcer	2 (4%)	-	-	2 (2%)
Macular hole	-	1 (4%)	1 (2%)	2 (2%)

Table 4

Comparison of Visual Acuity and Inflammation Score over Three Decades

	60's 89 eyes	80's 52 eyes	90's 94 eyes	
Mean logMAR (± S.E.) *		0.91 (0.071)	0.82 (0.092)	0.46 (0.069)
Mean Inflammation Score (± S.E.) *		1.2 (0.1)	0.5 (0.1)	0.5 (0.1)
Follow-Up Adjusted P-value for Difference in Visual Acuity between Decades **				
60's vs 80's	0.308			
60's vs 90's	<0.001			
80's vs 90's	0.019			
Follow-Up Adjusted P-value for Difference in Inflammation between Decades **				
60's vs 80's	<0.001			
60's vs 90's	<0.001			
80's vs 90's	0.618			

* S.E. is derived from a mixed model analysis that incorporated correlation between repeated measures within patient and between fellow eyes.

** P-values are from mixed models analysis with adjustment for follow-up time.

Table 5

Comparison of Systemic Treatment Employed in Patients with Ocular Behcet's Disease over 3 Decades

Medication	60's 45 patients	80's 26 patients	90's 49 patients	Total 120 patients
Systemic corticosteroids	43 (96%)	26 (100%)	41(84%)	110 (92%)
Systemic corticosteroids only	31(69%)	2 (8%)	8 (16%)	41 (34%)
Topical/periocular corticosteroids only	2 (4%)	0	4 (8%)	6 (5%)
Cyclosporine	0	23 (89%)	27 (55%)	50 (42%)
Daclizumab	0	0	15 (31%)	15 (13%)
Chlorambucil	6 (13%)	4 (15%)	4 (8%)	14 (12%)
Azathioprine	1 (2%)	2 (8%)	10 (20%)	13 (11%)
Methotrexate	2 (4%)	0	8 (16%)	10 (8%)
Mycophenolate mofetil	0	0	8 (16%)	8 (7%)
Infliximab	0	0	7 (14%)	7 (6%)
Cyclophosphamide	2 (4%)	3 (12%)	2 (4%)	7 (6%)
Sirolimus	0	0	1 (2%)	1 (1%)
6-mercaptopurine	1 (2%)	0	0	1 (1%)