Ocular Inflammation in Behçet Disease: Incidence of Ocular Complications and of Loss of Visual Acuity

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• PURPOSE: To estimate the risk of structural ocular complications and loss of visual acuity (VA) in cases of Behçet disease (BD) and to evaluate potential risk and protective factors for these events.

• DESIGN: Retrospective cohort study.

• METHODS: A total of 168 consecutive patients with BD-associated ocular inflammation treated at five academic center ocular inflammation subspecialty practices were included. Clinical data for these patients were ascertained by standardized chart review. Main outcome measures included VA, structural ocular complications of inflammation, and intraocular pressure (IOP).

• RESULTS: Over a median follow-up of 1.05 years, the incidence of specific structural complications and IOP disturbances were common: the incidence rate of any ocular complication was 0.45 per eye-year (EY). Rates of loss of VA to 20/50 or worse and to 20/200 or worse were 0.12 per EY and 0.09 per EY, respectively. Risk factors for loss of VA during follow-up were persistent inflammatory activity, presence of posterior synechiae, presence of hypotony, and presence of elevated IOP. In a time-dependent analysis, current activity of ocular inflammation was associated with an increased risk of loss of VA to 20/50 or worse (relative risk [RR], 2.45; 95% confidence interval [CI], 1.1 to 5.5; $P = .03$) and to 20/200 or worse (RR, 2.67; 95% CI, 1.2 to 5.8; $P = .01$).

• CONCLUSIONS: Loss of VA and occurrence of ocular complications were common in patients with ocular inflammation associated with BD, even with aggressive therapy. Ongoing inflammation during follow-up, presence or occurrence of posterior synechiae, hypotony, and elevated IOP were associated with an increased risk of loss of VA. (Am J Ophthalmol 2008;146:828–836.

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BEHÇET DISEASE (BD) IS A CHRONIC, RELAPSING INflammatory disorder of unknown origin. The first series of patients with BD was published in 1937[1] as a triad of symptoms consisting of oral aphthae, genital ulcers, and hypopyon iritis. BD is characterized by episodic inflammation that may affect every tissue and organ in the body.[2] The International Study Group for BD established the diagnostic criteria as recurrent oral aphthous ulcers plus two of the following: recurrent genital ulcers, ocular inflammation, skin involvement, and positive pathergy test results.[3] Ocular involvement occurs in approximately 70% of the patients and is associated with a high risk of blindness.[4] Ocular features of BD are anterior uveitis, retinal vasculitis (both veins and arteries), optic neuropathy, retinal infiltrates, scleritis, and vitritis. BD is more prevalent along the ancient Silk Road that extends from the Eastern Mediterranean to Japan. Men are affected more than women, with a two to 10:1 ratio in these countries.[5] Geographic variability in the clinical course is thought to exist, with a milder course and a reversal of the male-to-female ratio described in at least one Western population.[5]

Previous studies often have reported frequencies of complications over variable follow-up, an approach that can provide misleading results. Few true complication rates have been described. Also, little has been reported about the extent of specific structural complications causing loss of visual acuity (VA) over time in patients with BD in the United States, who may have a better prognosis than in populations along the ancient Silk Road.

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study is a retrospective cohort study conducted at five university-affiliated ocular inflammatory diseases subspecialty practices in the United States.[6] One of the aims of the study is to describe the outcomes of

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ocular inflammatory diseases. The purpose of this study was to assess the risk of loss of VA and of structural ocular complications in this large, Western cohort of patients with BD and ocular involvement and to evaluate potential risk factors for changes in VA.

METHODS

• **STUDY POPULATION:** The methods of the SITE Cohort Study have been described previously.[6] All patients with BD-associated ocular inflammation from the SITE cohort were included. These patients had been examined between January 1978 and December 2007 inclusive. The centers involved in the SITE Cohort Study are: the Uveitis Clinic, Casey Eye Institute, Oregon Health and Sciences University; the Laboratory of Immunology, National Eye Institute; the Ocular Immunology Service, Wilmer Eye Institute, Johns Hopkins University; the practice of C. Stephen Foster, formerly at the Massachusetts Eye and Ear Infirmary and now at the Massachusetts Eye Research and Surgery Institution; and the Ocular Inflammation Service, Scheie Eye Institute, University of Pennsylvania.

• **DATA COLLECTION:** Information on all patients evaluated and treated for BD-associated ocular inflammation was entered into a database using a computer-based standardized data entry form set specifically prepared for the SITE Cohort Study. The system includes extensive intrinsic quality control checks, requiring correction of potential errors in real time. Potential errors also were identified through post hoc range and logic checks, were investigated, and were rectified when appropriate. Data collected that are relevant to this report include: demographic characteristics, ophthalmologic examination findings, and all medications that patients (or eyes) were receiving at each clinic visit, including dose and route of administration. Ophthalmologic examinations included measurement of VA, intraocular pressure (IOP) assessment, and details regarding the activity and complications of the ocular inflammation. Retinal vasculitis was defined as active vascular sheathing seen in clinical examination, on fluorescein angiography, or both.

• **MAIN OUTCOME MEASURES:** Incidence rates for loss of or improvement in VA and for structural ocular complications and IOP disturbances were assessed. Loss or gain of VA was evaluated across the 20/50 or worse (visual impairment) and the 20/200 or worse (legal blindness) thresholds according to the recommendations of the Standardization of Uveitis Nomenclature Working Group[7]: improvement or worsening by three logarithm of the minimum angle of resolution (logMAR) lines also was evaluated, transforming Snellen VA measurements into logMAR equivalents,[8] when necessary.

Ocular complications evaluated included posterior synechiae, occurrence of cataract surgery, ocular hypertension (IOP $\geq$ 21 mm Hg and 30 mm Hg), hypotony (IOP $\leq$ 5 mm Hg), epiretinal membrane, macular edema, exudative retinal detachment, retinal neovascularization, and choroidal neovascularization.

• **STATISTICAL ANALYSIS:** Confidence intervals (CIs) on proportions were calculated assuming a binomial distribution. Incidence rates were calculated as the number of events divided by the amount of person-time or eye-time at risk. *P* values for proportions were calculated using the Chi-square test or Fisher exact test when expected cell counts were fewer than five. CIs on incidence rates were generated assuming a Poisson distribution. Potential risk factors for loss or gain of VA were evaluated using survival analysis, including Cox regression with adjustment for clustering between eyes of the same patient[9] (when applicable) to obtain adjusted risk ratios. Because vision loss events were exceedingly rare in the anterior uveitis only and other ocular inflammation groups, analyses for loss of VA were limited to the cases of BD-associated uveitis that had involvement of the posterior segment.

RESULTS

• **STUDY POPULATION AT PRESENTATION:** Demographic and clinical characteristics of the study population (168 patients and 317 affected eyes) are summarized in Table 1. The median follow-up time was 1.05 years (range, zero to 19.5 years). For the patients who had more than one visit, there were a total of 3,082 visits, with an average of 16.05 visits per person-year (PY) of follow-up. The median age at the time of diagnosis of uveitis was 31.3 for anterior uveitis and 27.6 for uveitis involving the posterior segment. Anterior uveitis was defined for the purpose of the study as the inflammation primarily in the anterior segment. Uveitis classified as intermediate using International Uveitis Study Group/Standardization of Uveitis Nomenclature (IUSG/SUN) criteria[7] was included with the posterior or panuveitis group, hereafter called the posterior involvement group. The anterior uveitis group comprised 18 (10.7%) of all patients, 10 (55.6%) of whom were male, as opposed to 67 (47.2%) of the posterior or panuveitis group. The nonuveitis group consisted of five patients with scleritis and one patient each with retrobulbar neuritis, orbital inflammation, and missing diagnosis. Bilateral ocular inflammation was present in 88% of the posterior segment cases vs 78% of anterior uveitis cases ($P = .26$). The median duration of uveitis before presentation to the referral center was three years for the anterior uveitis group and 2.2 years for the posterior segment group. Posterior synechiae were presentin 12.5% of anterior uveitis cases and in 8% of posterior segment cases at the time of presentation to the referral center. Retinal vascu-

TABLE 1. Characteristics of Patients with Behçet Disease at Presentation[a]

Characteristic	Anterior Uveitis Only	Uveitis Involving the Posterior Segment	Other
Person-specific characteristics			
No. of patients	18	142	8
Median age at diagnosis of uveitis, yrs (range)	31.3 (13.9 to 52.9)	27.6 (4.8 to 64.3)	30.4 (22.0 to 54.7)
Median age at diagnosis of Behçet disease, yrs (range)	37.9 (13.9 to 55.8)	28.3 (10.4 to 65.0)	26.7 (9.6 to 59.2)
Gender, % men	10 (55.6%)	67 (47.2%)	5 (62.5%)
Race			
% white	13 (72.2%)	87 (61.3%)	6 (75%)
% black	1 (5.6%)	16 (11.3%)	1 (12.5%)
% other	4 (22.2%)	39 (27.5%)	1 (12.5%)
Median duration of uveitis prior to presentation, years (range)	3.0 (0.0 to 23.6)	2.2 (0.0 to 30.5)	0.6 (0.0 to 12.2)
Bilateral uveitis, %	14 (77.8%)	125 (88.0%)	7 (87.5%)
Eye-specific characteristics			
No. of affected eyes	32	270	15
Ocular findings, % affected eyes			
Any ocular complication	13 (40.6%)	164 (60.7%)	3 (20%)
Posterior synechiae	4 (12.5%)	22 (8.2%)	0 (0.0%)
Retinal vasculitis	0 (0.0%)	59 (21.8%)	0 (0.0%)
Cataract surgery	2 (6.2%)	26 (9.6%)	0 (0.0%)
Ocular hypertension			
> 21 mm Hg	6 (18.7%)	35 (13%)	2 (13.3%)
> 30 mm Hg	1 (3.1%)	8 (3%)	0 (0.0%)
Hypotony	1 (3.1%)	2 (0.7%)	1 (6.7%)
Glaucoma surgery	0 (0.0%)	2 (0.7%)	0 (0.0%)
Epiretinal membrane formation	3 (9.4%)	31 (11.5%)	0 (0.0%)
Macular edema	2 (6.2%)	39 (14.4%)	0 (0.0%)
Exudative retinal detachment	0 (0.0%)	2 (0.7%)	0 (0.0%)
Retinal neovascularization	0 (0.0%)	6 (2.2%)	0 (0.0%)
Choroidal neovascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inflammatory activity, affected eyes, %			
Overall activity			
Inactive	22 (68.8%)	58 (21.5%)	7 (46.7%)
Slightly active	0 (0.0%)	61 (22.6%)	4 (26.7%)
Active	10 (31.3%)	151 (55.9%)	4 (26.7%)
Anterior chamber cell			
Data are missing	0 (0.0%)	5 (1.9%)	0 (0.0%)
No. of cells	22 (68.8%)	151 (55.9%)	12 (80.0%)
0.5+	2 (6.3%)	61 (22.6%)	2 (13.3%)
1.0+	4 (12.5%)	23 (8.5%)	0 (0.0%)
2.0+	4 (12.5%)	30 (11.1%)	1 (6.7%)
Vitreous cell			
Data are missing	2 (6.3%)	29 (10.7%)	0 (0.0%)
No. of cells	27 (84.4%)	59 (21.9%)	14 (93.3%)
0.5+	2 (6.3%)	53 (19.6%)	0 (0.0%)
1.0+	0 (0.0%)	62 (23.0%)	0 (0.0%)
2.0+ or worse	1 (3.1%)	67 (24.8%)	1 (6.7%)
Vitreous haze			
Data are missing	2 (6.3%)	66 (24.4%)	1 (6.7%)
None	27 (84.4%)	118 (43.7%)	13 (86.7%)
0.5+	2 (6.3%)	59 (21.9%)	0 (0.0%)
1.0+ or worse	1 (3.1%)	27 (10.0%)	1 (6.7%)
Visual acuity, % affected eyes			
20/50 or worse	8 (25.0%)	163 (60.4%)	5 (33.3%)
20/200 or worse	5 (15.6%)	92 (34.1%)	0 (0.0%)

Yrs = years.

[a]Other cases included five cases with scleritis and one case each with retrobulbar neuritis, orbital inflammation, and missing types of ocular inflammation. Fourteen subjects' date of Behçet disease diagnosis was missing, so an age at diagnosis could not be calculated.

TABLE 2. Incidence of Structural Ocular Complications and of Visual Acuity Loss in Eyes with Behçet Disease

Event	Person			Eye		
	No. of Events/No. of Persons at Risk	Person Years	Rate per Person Years (95% Confidence Interval)	No. of Events/No. of Affected Eyes at Risk	Eye Years	Rate per Eye Year (95% Confidence Interval)
Ocular findings						
Any ocular complication	41/45	8.44	4.86 (3.49 to 6.59)	70/90	156.03	0.45 (0.35 to 0.57)
Posterior synechiae	25/98	359.67	0.07 (0.05 to 0.10)	38/201	791.29	0.05 (0.03 to 0.07)
Retinal vasculitis	40/83	235.61	0.17 (0.12 to 0.23)	67/172	545.55	0.12 (0.09 to 0.16)
Cataract surgery	32/113	376.68	0.09 (0.06 to 0.12)	31/205	878.52	0.04 (0.02 to 0.05)
Ocular hypertension						
≥ 21 mm Hg	52/93	216.17	0.24 (0.18 to 0.32)	89/192	528.27	0.17 (0.14 to 0.21)
≥ 30 mm Hg	30/110	438.77	0.07 (0.04 to 0.1)	37/214	898.63	0.04 (0.03 to 0.06)
Rise of 10 mm Hg	46/123	362.1	0.13 (0.09 to 0.17)	78/376	1401.51	0.06 (0.04 to 0.07)
Hypotony	8/111	517.83	0.02 (0.01 to 0.03)	8/216	1008.59	0.01 (0.003 to 0.02)
Glaucoma surgery	3/115	524.09	0.006 (0.001 to 0.02)	4/219	1001.57	0.004 (0.001 to 0.01)
Epiretinal membrane formation	44/97	300.47	0.15 (0.11 to 0.20)	75/198	665.69	0.11 (0.09 to 0.14)
Macular edema	49/93	217.12	0.23 (0.17 to 0.3)	71/188	527.41	0.14 (0.11 to 0.17)
Exudative retinal detachment	6/115	525.47	0.01 (0.004 to 0.03)	6/220	1016.22	0.006 (0.002 to 0.01)
Retinal neovascularization	7/111	491.81	0.01 (0.006 to 0.03)	6/214	971.96	0.006 (0.002 to 0.01)
Choroidal neovascularization	2/115	549.27	0.004 (0.000 to 0.01)	2/220	1040.02	0.002 (0.0 to 0.007)
Visual acuity change						
To 20/50 or worse	18/33	86.27	0.21 (0.12 to 0.33)	35/94	284.31	0.12 (0.09 to 0.17)
To 20/200 or worse	24/59	162.49	0.15 (0.1 to 0.22)	43/147	471.11	0.09 (0.07 to 0.12)
Loss of 3 lines	93/114	141.22	0.66 (0.53 to 0.81)	71/138	341.38	0.21 (0.16 to 0.26)
Gain of 3 lines	71/114	185.41	0.38 (0.3 to 0.48)	95/203	450.64	0.21 (0.17 to 0.26)

litis and macular edema were the most common ocular findings present in posterior segment group eyes (22% and 14%, respectively). Among patients with posterior involvement, approximately 10% already had undergone cataract surgery compared with 6% of anterior uveitis eyes ($P = .75$). Elevated IOP of 21 mm Hg or more was present in 19% of the eyes with anterior uveitis, compared with 13% of posterior or panuveitis eyes ($P = .41$). Reduced VA was common in both groups, but was more common in the eyes with posterior segment involvement, with 25% of the anterior uveitis eyes and 60% of the posterior uveitis eyes having a VA of 20/50 or worse at presentation ($P = .0001$). A similar pattern was observed for VA of 20/200 or worse: 16% for the anterior uveitis cases and 34% for the posterior involved cases ($P = .035$).

• **INCIDENCE OF STRUCTURAL OCULAR COMPLICATIONS AND OF VISION LOSS OR GAIN:** The incidence rates for ocular complications and loss of VA among cases with posterior involvement are given as Table 2. The incidence of retinal vasculitis during follow-up was 0.17 per PY among patients without retinal vasculitis at presentation or 0.12 per eye-year (EY) among eyes with inflammation but free of vasculitis at presentation. Incidence of ocular hypertension (≥ 21 mm Hg) was 0.24 per PY or 0.17 per EY, and that for IOP of 30 mm Hg or more was 0.07 per PY or 0.04 per EY. The rate of macular edema during follow-up was 0.23 per PY or 0.14 per EY. The incidence rates of loss of VA to 20/50 or worse and to 20/200 or worse among affected eyes were 0.12 per EY and 0.09 per EY, respectively, among eyes with VA better than these thresholds at presentation. The incidence of gaining three lines of VA during follow-up was 0.38 per PY or 0.21 per EY.

• **RISK FACTORS FOR VISUAL ACUITY LOSS AMONG EYES AFFECTED BY BEHÇET DISEASE:** Risk factors for loss of VA are summarized in Table 3. In the time-dependent multiple regression analysis, current presence of anterior chamber (AC) cell ≥ 1+, vitreous cell ≥ 2+, vitreous haze ≥ 1+, hypotony, and elevated IOP were associated with a statistically significant increased risk of VA loss to 20/50 or worse. The analysis for loss of VA to 20/200 or worse identified a similar set of risk factors, including the current presence of AC cell ≥ 2+, vitreous cell ≥ 1+, vitreous haze ≥ 1+, posterior synechiae, and hypotony. The relationship between measures of current (time-updated) inflammatory activity and loss of VA are depicted in Figure 1 (relationship to overall activity) and Figure 2 (relationship to vitreous haze). Overall activity of inflammation was associated with an increased risk of loss of VA to 20/50 or worse (relative risk [RR], 2.45; 95% CI, 1.1 to 5.5; $P = .03$) and to 20/200 or worse (RR, 2.67; 95% CI, 1.2 to 5.8; $P = .01$). Measures assessing a broader range of inflammatory activity were associated more strongly with increased risk of vision loss. The presence of AC cell ≥ 2+

TABLE 3. Risk Factors for Loss of Visual Acuity in Eyes with Behçet Disease[a]

Characteristic Name	Crude Relative Risk 20/50 or Worse (95% Confidence Interval; *P* value)	Adjusted Relative Risk 20/50 or Worse (95% Confidence Interval; *P* value)	Crude Relative Risk 20/200 or Worse (95% Confidence Interval; *P* value)	Adjusted Relative Risk 20/200 or Worse (95% Confidence Interval; *P* value)
Age at uveitis diagnosis (10 yrs)	1.1 (0.8 to 1.5; .47)	1.1 (0.8 to 1.45; .60)	1.1 (0.8 to 1.4; .63)	1.1 (0.8 to 1.55; .55)
Male gender	1.3 (0.7 to 2.7; .43)	1.2 (0.6 to 2.4; .65)	1.2 (0.6 to 2.3; .65)	1.2 (0.6 to 2.7; .61)
Race				
White	1.00	1.00	1.00	1.00
Black	0.7 (0.2 to 2.8; .62)	0.8 (0.2 to 2.9; .70)	0.4 (0.1 to 1.3; .12)	0.4 (0.1 to 1.1; .06)
Other	2.0 (1.0 to 4.2; .06)	1.9 (0.9 to 4.1; .09)	1.1 (0.5 to 2.4; .80)	0.9 (0.4 to 2.1; .84)
Uveitis time to presentation	1.0 (0.9 to 1.1; .84)	1.0 (0.9 to 1.1; .75)	1.0 (0.9 to 1.04; .44)	1.0 (0.9 to 1.03; .38)
Time-dependent characteristics				
Bilateral	0.4 (0.1 to 1.9; .22)	0.2 (0.04 to 1.1; .07)	0.4 (0.1 to 0.9; .03)	0.3 (0.1 to 0.8; .02)[b]
Overall activity[c]				
Inactive	1.00	1.00	1.00	1.00
Slightly active	0.8 (0.2 to 2.6; .69)	0.8 (0.2 to 2.6; .65)	1.2 (0.5 to 3.2; .72)	0.9 (0.3 to 2.8; .87)
Active	2.5 (1.2 to 5.2; .02)	2.5 (1.1 to 5.5; .03)[b]	3.0 (1.5 to 6.0; .002)	2.7 (1.2 to 5.8; .01)[b]
Anterior chamber cell				
No cells	1.00	1.00	1.00	1.00
0.5+	2.0 (0.8 to 4.9; .12)	1.9 (0.7 to 4.7; .19)	1.9 (0.9 to 3.8; .08)	1.7 (0.9 to 3.5; .13)
1.0+	3.2 (0.9 to 12.0; .08)	3.7 (1.0 to 13.1; .04)[b]	2.2 (0.3 to 14.2; .43)	2.2 (0.3 to 15.0; .41)
2.0+ or worse	3.3 (0.8 to 13.0; .09)	4.1 (1.0 to 16.9; .05)[b]	3.3 (1.1 to 10.4; .04)	4.7 (1.2 to 18.6; .03)[b]
Vitreous cell				
No cells	1.00	1.00	1.00	1.00
0.5+	2.2 (0.8 to 6.4; .15)	1.9 (0.6 to 6.3; .31)	0.3 (0.06 to 1.2; .08)	0.2 (0.04 to 1.1; .06)
1.0+	3.3 (1.1 to 9.7; .03)	3.1 (0.9 to 10.5; .06)	3.5 (1.6 to 7.8; .002)	3.1 (1.4 to 7.0; .006)[b]
2.0+ or worse	3.7 (1.1 to 12.4; .04)	4.6 (1.3 to 15.7; .02)[b]	3.2 (1.2 to 8.7; .02)	2.8 (1.0 to 8.3; .06)
Vitreous haze				
None	1.00	1.00	1.00	1.00
0.5+	2.2 (0.9 to 5.5; .09)	2.3 (0.9 to 6.1; .09)	2.0 (0.8 to 5.2; .16)	1.5 (0.5 to 4.7; .50)
1.0+ or worse	6.2 (3.2-12.2; < .0001)	12.0 (2.1 to 68.7; .005)[b]	5.3 (1.7 to 16.6; .005)	7.4 (2.5 to 21.8; .0003)[b]
Posterior synechiae	Insufficient data	Insufficient data	3.73 (1.4 to 10.23; .01)	3.04 (1.07 to 8.61; .04)[b]
Retinal vasculitis	0.8 (0.4 to 1.6; .45)	0.7 (0.3 to 1.6; .45)	1.2 (0.6 to 2.2; .65)	1.2 (0.6 to 2.2; .70)
Hypotony	6.8 (0.9 to 52.5; .07)	19.9 (3.2 to 124.1; .001)[b]	9.2 (1.8 to 47.6; .009)	24.6 (9.6 to 63.2; < .0001)[b]
Elevated IOP	3.5 (1.6 to 8.0; .003)	5.3 (1.2 to 23.6; .03)[b]	1.4 (0.6 to 2.9; .44)	1.8 (0.7 to 4.5; .24)
Prior cataract surgery	2.2 (0.8 to 6.4; .14)	2.4 (0.7 to 8.8; .17)	1.4 (0.6 to 3.7; .45)	2.6 (0.7 to 10.0; .18)
Prior glaucoma surgery	0.7 (0.1 to 6.7; .74)	0.6 (0.04 to 9.6; .74)	0.7 (0.1 to 5.5; .71)	1.0 (0.1 to 7.5; .96)

IOP = intraocular pressure; yrs = years.

[a]Adjusted for age, gender, race, duration of uveitis before presentation, and overall activity to worse than 20/200; also includes bilateral uveitis. Location of inflammation was omitted because no cases of vision loss occurred in the anterior uveitis group.

[b]Statistically significant data.

[c]Active vs slightly or inactive significant in adjusted models 20/50 (2.62 to 0.1), 20/200 (2.74 to 0.007). Other inflammatory activity variables were excluded from models providing adjusted estimates of relative risk for the indicators of inflammatory activity (activity, anterior chamber cells, vitreous cells, and vitreous haze).

was associated with a four-fold increase in the incidence of VA of 20/50 or worse (RR, 4.1; 95% CI, 1 to 16.9; $P = .05$), and with an almost five-fold increase in the incidence of VA of 20/200 or worse (RR, 4.7; 95% CI, 1.2 to 18.6; $P = .03$). The presence of vitreous haze ≥ 1+ was associated with a 12-fold increase in the incidence of VA of 20/50 or worse (RR, 12.0; 95% CI, 2.1 to 68.7; $P = .005$) and a more than seven-fold increase in developing VA of 20/200 or worse (RR, 7.4; 95% CI, 2.5 to 21.8; $P = .0003$).

In general, higher risk of loss of VA occurred in a dose-response pattern with increasing levels of intraocular inflammation, which was consistent across different measures of inflammatory activity. The most common causes of VA loss for both outcomes were inflammatory haze, cataract, cystoid macular edema (CME), macular scar formation, and optic nerve disease (see Table 4).

DISCUSSION

IN PREVIOUS REPORTS FROM COUNTRIES WITH A HIGH incidence of BD (Turkey and Japan), the risk of blindness

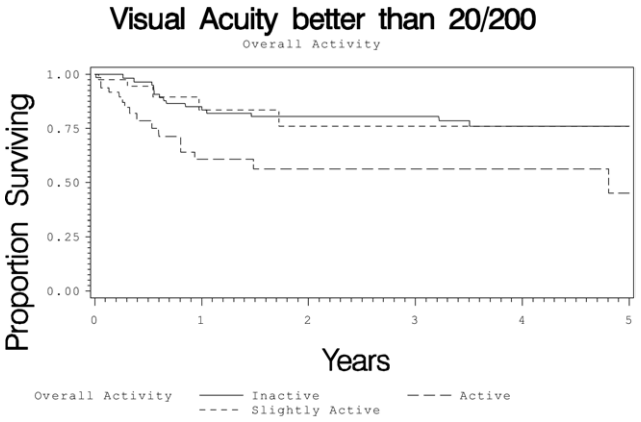

FIGURE 1. Kaplan-Meier survival curve demonstrating the loss of visual acuity (VA) to the 20/200 or worse level over time, in relationship to current (time-updated) overall activity of uveitis. Slightly active refers to minimal signs of activity, which cannot be graded properly as the absence of active inflammation according to Standarization of Uveitis Nomenclature criteria.[7] Follow-up is truncated at five years; events were rare after the first five years.

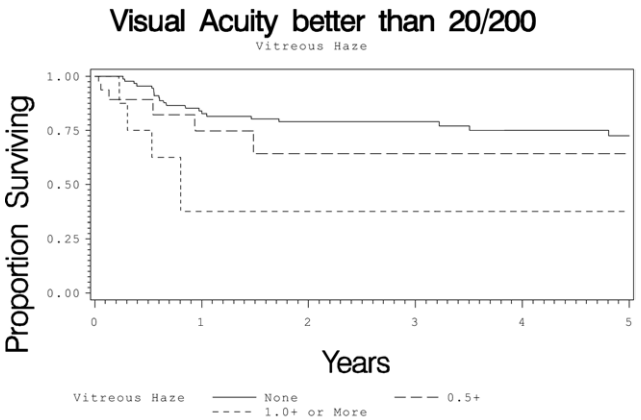

FIGURE 2. Kaplan-Meier survival curve demonstrating the loss of VA to the 20/200 or worse level over time, in relationship to current (time-updated) level of vitreous haze. Follow-up is truncated at five years; events were rare after the first five years.

among patients with BD-associated uveitis was high: patients were observed to become blind in an average of 3.36 years after the onset of eye symptoms[10] and to reach a VA of 20/200 or worse within four years in 50% to 90% of cases.[11] However, the prevalence of legal blindness was reported to be 25% in North America,[12] and Muhaya and associates found significant differences in the severity of ocular involvement between patients in Japan and Great Britain.[13] Our results suggest that there is a high risk of loss of VA in patients in the United States, as well.

With the availability of new therapeutic approaches, this ominous outlook may be improving. Nevertheless, BD-associated uveitis still bears a guarded visual prognosis

TABLE 4. Primary Cause of Visual Acuity Loss in Eyes Affected by Behçet Disease

Cause	20|50 or Worse (n = 211)	20|200 or Worse (n = 140)
Inflammatory haze	73 (34.6%)	48 (34.3%)
Cataract	26 (12.3%)	18 (12.9%)
Cystoid macular edema	14 (6.6%)	9 (6.4%)
Macular scar	7 (3.3%)	7 (5.0%)
Optic nerve disease	10 (4.7%)	6 (4.3%)
Epiretinal membrane	11 (5.2%)	4 (2.9%)
Glaucoma	2 (0.9%)	2 (1.4%)
Posterior capsular opacification	0 (0.0%)	2 (1.4%)
Noninflammatory disease	3 (1.4%)	0 (0.0%)
Retinal neovascularization	1 (0.5%)	1 (0.7%)
Corneal sequelae of inflammation	1 (0.5%)	1 (0.7%)
Choroidal neovascularization	0 (0.0%)	0 (0.0%)
Phthisis	0 (0.0%)	0 (0.0%)
Other	32 (15.2%)	23 (16.4%)
Missing	28 (13.3%)	19 (13.6%)
No cause identified	3 (1.4%)	0 (0.0%)

with a high risk of cataract, CME, macular scar formation, and optic nerve disease, among others.

The age of uveitis in our American cohort, approximately 30 years of age, was similar to that reported in other parts of the world: 34 years for both genders in Japan[14,15] and 28.5 years for males and 30 years for females in Turkey.[16] We did not observe a strong male preponderance, in contrast to what has been reported from the countries along the ancient Silk Road.[15–17] Males comprised 63% of all patients in Japan[14] and 68% of all patients in Turkey.[16] However, one report from Israel showed less male preponderance at 53% of all patients,[18] and a report from Italy had a population with an even distribution (50%) in gender,[19] observations similar to ours.

We used rates of a specific outcome such as VA calculated per PY or per EY, instead of final visit statistics, to limit the bias of variable follow-up time and to facilitate subsequent comparisons across different studies as recommended by the Standardization of Uveitis Nomenclature Guidelines.[7] Although the median follow-up time of 1.05 years may seem to be short, the PY and EY numbers are quite large, ranging from 86.3 to 549.3 PYs and 284.3 to 1401.5 EYs. Because most of the older reports did not use this approach, it is difficult to compare our results precisely with those of the other reports. In some of our analyses, the number of events was small, which limited the precision of RR estimates for certain risk factors. Nonetheless, the study suggests that the development of loss of VA and structural ocular complications are very frequent in BD-associated uveitis involving the posterior segment, but not highly frequent when disease is limited to anterior uveitis or scleritis. Some form of ocular complication occurred in nearly half of the eyes with posterior segment involvement during each year of follow-up.

Visual acuity loss during BD flare-ups may be reversible after treatment. We observed an incidence rate of 0.21 per EY and 0.38 per PY of gaining three lines in the Snellen chart in this cohort, which supported this fact. To deal with the problem of reversibility, an event for VA loss was defined as VA $\leq$ 20/200 at two or more visits spanning 30 days to approximate irreversible vision loss.

One of our most striking observations was a consistent dose-response relationship between the current (time-updated) inflammatory activity and risk of loss of VA. This result confirms a principle that is widely understood in the field of uveitis, although it has been confirmed objectively only occasionally[16,20,21]: that control of active inflammation is critically important to avoid vision loss in patients with BD-associated uveitis. Current (time-updated) presence of posterior synechiae also was associated with an increased risk of loss of VA, probably representing to some extent the cumulative damage an eye had sustained as a result of inflammation up to that point. Disturbances of IOP—particularly hypotony, but also ocular hypertension—were associated with substantially increased risk of vision loss, suggesting that both preventive and corrective therapy for these problems are an important aspect of the management of patients with BD-associated uveitis.

In this nonrandomized study, we were unable to assess directly the merits of alternative forms of therapy for BD-associated uveitis because disease severity seemed to be strongly related to the choice to use more aggressive forms of therapy. However, the benefit of treatment sufficiently aggressive to control ocular inflammation can be inferred by the strong dose-response relationship between the current level of inflammation and risk of loss of VA, as well as from the observation that in a substantial group of patients and eyes, visual improvement developed while under management. Yoshida and associates reported significant improvements in visual prognosis with the use of immunosuppressive therapy,[15] an approach we believe to be well justified for a disease with as poor a visual prognosis as BD-associated uveitis involving the posterior segment. This approach also is supported by other randomized clinical trials.[22,23] However, more randomized studies would be needed to identify clearly the best specific approach to management of these cases, which may be a combination therapy of various agents.[24] Among the currently popular approaches to management are the uses of infliximab[25,26] and of interferon-α.[27]

Additional limitations of the study are that a referral bias may exist, because all five institutions are tertiary care centers, and it is likely that relatively severe cases of BD-associated ocular inflammation tended to be referred to these centers, as suggested by high frequencies of ocular complications and poor VA at presentation. The frequency of reduced VA at presentation (VA of 20/200 or worse in 34% of posterior or panuveitis patients and in 16% of anterior uveitis patients) was similar to that reported from other tertiary care centers along the ancient Silk Road. Yoshida and associates reported that 37% of the patients seen in the 1980s had poor VA (20/200 or worse) at the first visit.[15] Tugal-Tutkun and associates reported that 41% of the patients had an initial VA of 20/200 or worse.[16] Also, it has been suggested that the first two years after the diagnosis are the most critical for the visual prognosis of patients with BD-associated uveitis,[28] in which case our results may not fully reflect the potential benefits of therapy, because most patients were referred more than two years after diagnosis. Based on these considerations, the prognosis of BD-associated ocular inflammation in the total population of persons with this condition is probably better than we observed, but our observations are probably generalizable to other tertiary uveitis centers.

In summary, moderate and severe visual impairment as well as structural ocular complications occurred commonly in this cohort of patients with BD-associated ocular inflammation, despite typically aggressive management often including immunosuppressive therapy. The presence of posterior synechiae, persistence of higher grades of intraocular inflammation, elevated IOP, and hypotony were statistically significant factors for the development of vision loss after controlling for other potentially confounding variables. The most common causes of incident loss of VA during follow-up were inflammatory haze, cataract, and macular disorders, all of which are potentially treatable or preventable causes of poor vision. Increased activity of inflammation is associated with increased risk of loss of VA in a dose-dependent fashion, providing reinforcement to the message that treatment adequate to control inflammation is of preeminent importance in patients with BD-associated ocular inflammation.

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(Wilmer/JHU); New England Institutional Review Board (MERSI); Massachusetts Eye & Ear Infirmary Institutional Review Board (MEEI); Oregon Health & Sciences University Institutional Review Board (Casey/OHSU); Combined Neurosciences (CNS) Institutional Review Board of the Clinical Center (CC), National Eye Institute. The study was conducted in accordance with the precepts of the Declaration of Helsinki.

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AJO History of Ophthalmology Series

Many Forms of Neurosyphilis

Neurosyphilis took its toll on many accomplished people of the time, among them the great German poet, Heinich Heine (1797 to 1856). In 1837, he developed a violent ocular pain and became blind in the left eye. He developed a ptosis on one side, then the other, and had to prop open his lids with his fingers. He then developed progressive paralysis and other problems most consistent with tabes dorsalis. His mind remained clear and he wrote memorable poems until almost his last breath.

Cerebral lues also affected Guy de Maupassant (1850 to 1893), the famous French writer. He developed hallucinations during which he felt his thoughts had escaped his head and were flitting about as highly colored butterflies: "black. . .for sadness, pink. . .for merriment, red. . .for adultery." An observer saw him make gestures as though trying to catch them as they flew.

Provided by Ronald Fishman, MD, of the Cogan Ophthalmic History Society.