Causes of Blindness in Ocular Behçet's Disease
Comparing the End-Blinding Results in Two Genders

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Abstract

***Purpose*:** To investigate and compare the causes of blindness in ocular Behçet's disease (BD) in men and women

***Methods*:** In a retrospective, descriptive investigation from 1976 to 2008, 6,021 BD cases were registered in our BD Unit of Shariati Hospital of Tehran University of Medical Sciences (TUMS). At the last visit, 187 patients (124 men and 63 women) were blind (vision=$^1/_{10}$ or less) at least in one eye and with at least 3 years of follow-up in our clinic. All patients received conventional treatments for BD following the diagnosis.

***Results*:** 187 unilateral or bilateral blind cases of BD, 124 males (244 eyes) and 63 females (124 eyes) were included in our study. They were blind (VA=$^1/_{10}$ or less) at the last visit. The mean age of men was 31.74±8.6 years, the mean age of women was 33.13±10.26 years at presentation, t=0.97, P=0.3. At presentation 229 eyes (62.23%) had severely impaired vision (VA≤$^1/_{10}$), 144 eyes (59.02%) of men and 85 eyes (68.55%) of women, χ^2 =0.403, P=0.5. The mean duration of diagnosis up to 2008 was 13.85±6.42 years in men and 15.65±6.41 years in women, t=1.8, P=0.05. The end-blinding outcome was registered in 77.99% (N=287) eyes, 78.28% (N=191) eyes in men and 77.42% (N=96) eyes in women. χ^2 =0.05, P=0.8. The most common cause for blindness was end-stage disease (retinal vascular necrosis or fibrosis, chorioretinal and optic atrophy) which was observed in 39.67% (N=146) eyes, 40.98% (N=100) eyes of men and 37.09% (N=46) eyes of women, χ^2 -0.163, P=0.7.

***Conclusion*:** BD can have a very severe and blinding outcome, but the end blinding result does not seem to be different in two genders.

***Keywords*:** Behçet's disease, Retinal Vascular Necrosis, Chorioretinal Atrophy, Optic Atrophy-Blindness

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Introduction

Behçet's disease (BD) is a chronic inflammatory and necrotizing vasculopahy with unpredicted recurrences and remissions. It is a disease which involves almost all organs.[1] The disease was originally expanded along the silk road, from China to North Africa, but actually due to the immigration of people can be seen all over the world.[2] The prevalence of the disease is variable in different countries. In Turkey the rate has been reported to be the highest 370 for 100,000 inhabitants.[3] In Iran[4] the prevalence has been reported to be 80 and in USA[5] 8.6 per 100,000 inhabitants.

The etiopathogenesis of the disease is unclear. The diagnosis of the disease is made mainly by the clinical symptoms of BD. The major criteria and their reported incidences in Iranian patients are as follows[6] : oral aphthosis (97%), genital aphthosis (65%), skin lesions (67%), ocular manifestations (56%). The minor criteria of BD are less frequent which are cardiovascular, articular, gastrointestinal, pulmonary, neurological, etc.

There are several proposed diagnostic criteria to distinguish BD. The most recent proposition is the International Criteria (ICBD)[7] which is actually mostly used.

In the five existing nationwide survey (Iran, Japan, China, Korea and Germany)[8] the male to female ratio of BD has been estimated to be 1.1 male to 1 female. In most publications the ocular involvement in BD has been reported to be considerably more frequent in the male population. In the recent report by Davatchi et al[9] of 4,717 BD cases, 62% of men versus 49% of women had ocular involvement (χ^2 =105.95, P=0.000). Hamzoui et al[10] reported the ocular involvement in 32.2% of BD patients (37.5% of men versus 17.8% of women). Not only the ocular BD has been reported to be more frequent in men but for many authors the course of the ocular disease has been considered to be more severe and sight threatening in men.[10-13]

In this present study we have investigated the ocular manifestations of BD and compared the blinding outcome in two sexes.

Methods

This study was performed in August 2008 at Shariati Hospital of Tehran University of Medical Sciences which is a tertiary referral center for BD patients. From 1976 to 2008, 6,021 BD patients were registered in our BD Unit. At the last visit in our center 267 patients were legally blind (VA≤$^1/_{10}$) in one or both eyes. 187 cases with at least three years of follow-up were included for this investigation, and the remaining 80 blind cases with less than three years of follow-up were excluded.

The medical files and ophthalmic charts of the blind patients were reviewed. The charts were prepared in 1976 and contained the complete ophthalmic data concerning ocular symptoms of the patients. The charts were filled at each visit. The needed information from the charts were extracted. The data collection for this study was approved by the ethical committee of our university.

In this retrospective, descriptive study 187 unilateral or bilateral blind BD cases (at the last visit) have been investigated, 124 men (244 eyes) and 63 women (124 eyes). After the diagnosis of BD the patients were visited at least twice yearly. None of these patients had a conventional treatment for BD before consulting our clinic. After the diagnosis of BD, the patients were put under 0.5 mg/kg/daily of corticosteroids which was gradually adjusted to the patients need. Immunosuppressors and/or modulators were also used at the same time (Table 1). The treatment protocol changed during the follow-up period according to the response of the patient and according to the disposition of the new drugs.

The visual acuity (VA) was measured by Snellen chart converted to logMAR for statistical analysis. The eyes were examined by Haag-Streit biomicroscopy, 3M of Goldmann or indirect ophthalmoscopy. Fluorescein angiography, sonography and in recent years optical coherence tomography were used if needed. The diagnosis of BD was achieved initially by the Japanese diagnostic criteria of BD[14] later on by the classification tree of BD,[15] and in 2008 were all confirmed by the International Classification of BD.[7]

The duration of diagnosis of BD was calculated from the first visit in our clinic up to 2008.

The duration of follow-up was calculated from the time of diagnosis up to the last visit in our clinic. The period between the onset of the

first symptom and the diagnosis of BD was considered as the lag time.

The term retinal vasculitis was applied when the sheathing, fibrosis or necrosis of the retinal vessels was seen directly by ophthalmoscopy.

We define retinitis as small ($^1/_{4^{th}}$ to 1 mm) foci of whitish cotton-wool like elevations on central but mostly peripheral retina, surrounded by inflammatory cells and presenting leakage on fluorescein angiography.

Three eyes in men and two in women were phthisic or enucleated at presentation, therefore they were not included in some of our calculations. In four cases in men and two in women the ocular disease was unilateral, therefore only the diseased eye was included in our analysis.

Data were analyzed using χ^2 and one way ANOVA tests with SPSS 11.5. P value of 0.05 or less has been considered significant.

Results

187 BD patients (124 males and 63 females), legally blind unilaterally or bilaterally at the last visit in our clinic and with at least three years of follow-up were investigated. The end blinding manifestations are compared in two sexes.

The mean age of the patients at presentation for men was 31.74±8.6 years and for women was 33.13±10.26, t=0.97, P=0.3.

The duration of diagnosis of BD, the duration of follow-up and the lag time for diagnosis of BD are indicated in Table 2.

At presentation 229 eyes (62.23%) had the VA of $\leq^1/_{10}$, 144 eyes (59.02%) in men and 85 eyes (68.55 %) in women, t=0.4, P=0.5, at the final visit 191 eyes (78.3%) in men and 96 eyes (77.4%) in women were legally blind (Table 3). Although, at the last visit the number of the eyes which had lost their useful vision and had become blind ($VA\leq^1/_{10}$), despite our intensive treatments was higher in men, 47 eyes (19.3%) versus 11 eyes (8.9%) in women, but the difference was not statistically significant, χ^2 =0.759, P=0.4. The initial and final mean vision of the two sexes are indicated in Table 3. Initially the mean vision of men was significantly higher than women, P=0.01, but at the end of the study the difference was insignificant, P=0.9.

The ocular manifestations of the patients during the follow-up are indicated in Table 4.

Uveitis was seen in 94.76 % of eyes (344 of 363 eyes), in 93.76% of eyes of men and in 96.72% of eyes of women, P=0.5 (Table 4). The duration of uveitis was 4.91±4.64 years in men and 4.32±3.26 years in women, t=1.28, P=0.2. Uveitis appeared in recurrences in different segments of the eye and seldom remained persistant. During the years of follow-up, panuveitis was the most frequent form of uveitis which was seen in 73.8% (N=268 of 363 eyes), 71.78 % in men and 77.87 % in women, P=0.55. Isolated vitritis was seen in 15.9% (N=58 eyes), 6% (N=43 eyes) of men and 12.3% (N=15 eyes) of women, P=0.5, and isolated anterior uveitis without vitreous involvement was seen in 18 eyes (4.9%), 10 eyes (4.9%) in men and 8 eyes (6.56%) in women, P=0.5.

Retinal vasculitis was observed via ophthalmoscopy in 80.44% (N=292 of 363 eyes) of the patients, 81.74% (N=197 of 241 eyes) of men and 77.87% (N=95 of 122 eyes) of women, t=0.242, P=0.6. The duration of retinal vasculitis was 5.69±5.36 years in men and 6.36±6.20 years in women, t=1.030, P=0.3.

Retinal vasculitis appeared in recurrences and involved different branches of veins and arteries. Later on it remained constant and progressive. Some rare manifestations were more frequent in men: glaucoma 12 for 2, phthisis bulbi 8 for 4, retinal detachment 8 for 4, retinitis 3 for 2, branch or central vein occlusion 4 for 1, optic neuritis 3 for 1, fundus neovascularization 3 for 1, and vitreous hemorrhage was seen in 2 men and macular hole was observed only in one man.

The end blinding manifestations ($Vision\leq^1/_{10}$) are indicated in Table 5. The most frequent cause of blindness was end-stage disease (Figure 1) which was more frequent in men 40.98% (N=100) and 37.09% (N=46) eyes in women, P=0.7, which was followed by macular scar 14.34% (N=35) eyes in men and 18.54% (N=23) eyes in women, P=0.6.

The rare causes of blindness which were all more frequent in men are as follows: glaucoma 8 for 1, cystoids macular edema 3 for 1, retinal vein occlusion 3 for 1, macular hole and vitreous hemorrhage one case of each in men.

Finally, at the end of the follow-up the percentage of blind eyes were more or less equal in both sexes 78.28% (N=191 eyes) of men versus 77.42% (N=96 eyes) of women, P=0.8 (Table 3).

Table 1. Treatment of Behçet's Disease patients during the follow-up, 124 men and 63 women. They all had corticosteroid associated with their treatment.

Regimen	Men		Women	
	N	(%)	N	(%)
Cyclophosphamide	117	94.3	47	74.6
Methorexate	96	77.4	35	55.5
Azathioprin	38	30.6	21	33.3
Levamisole	33	26.6	17	26.9
Ciclosporin	27	21.7	3	4.7
Imuran	15	12.1	7	11.1
Chlorambucil	15	12.5	8	12.7
Prednisolone alone	9	7.2	0	0
Leukeran	4	3.2	4	3.2

Table 2. Demographic and characteristics of 187 blind Behçet's Disease patients, 124 men and 63 women

	Men	Women	t	P
Mean age	31.74±8.6	33.13±10.27	0.97	0.3
Duration of disease up to 2008	18.4±8.03	20.5±7.75	1.71	0.07
Lag time	4.65±4.56	5.44±4.49	1.13	0.2
Duration of diagnosis up to 2008	13.85±6.42	15.65±6.4	1.18	0.06
Duration of follow-up	9.88±6.16	11.38±6.87	1.15	0.2

All dates are expressed in year.

Table 3. Initial and final vision of 187 Behçet's Disease cases (368 eyes), 124 men (244 eyes), 63 women (124 eyes)

Vision	Men	Women	t , χ^2	P
	Eyes (%)	Eyes (%)		
Initial mean VA	1.16±0.97	1.44±1.12	2.57	0.01
Final mean VA	2.03±1.36	2.05±1.36	0.13	0.9
Initial impaired VA	144 (59.0)	85 (68.5)	0.40	0.5
Final impaired VA	191 (78.3)	96 (77.4)	0.05	0.8

Impaired vision: VA of ≤1/10
VA: Visual acuity

Table 4. Major ocular manifestations of 187 Behçet's Disease patients, 124 males and 63 females, blind at the last visit, during the follow-up

	Total		Men		Women		χ^2	P
	Eyes	(%)	Eyes	(%)	Eyes	(%)		
Eyes	363	(100)	241	(66.4)	122	(33.6)		
Uveitis	344	(94.8)	226	(93.8)	118	(96.7)	0.59	0.5
Ret vascul	292	(80.4)	197	(81.7)	95	(77.9)	0.24	0.6
Cataract	282	(77.7)	179	(74.3)	103	(84.4)	0.58	0.5
White disc	218	(60.0)	148	(61.4)	70	(57.4)	0.17	0.7
Post scar	219	(60.3)	139	(57.7)	76	(62.3)	0.19	0.7
Macul ede	212	(58.4)	135	(56.0)	77	(63.1)	0.29	0.6
Disc ede	132	(36.4)	85	(34.8)	48	(39.3)	0.19	0.7

Ret vasculitis: Rretinal vasculitis, White disc: Partial or total optic atrophy, Post scar: Macular or paramacular scar, Ede: Edema
3 eyes in men and 2 eyes in women have been enucleated or phthisic at presentation not encountered in our statistics, and four men and two women have had unilateral ocular disease and one eye of them has not been included in our calculations.

Table 5. End-blinding results of 187 Behçet's Disease patients (368 eyes), 124 males (224 eyes), 63 females (124 eyes)

Cause	Total		Men		Women		χ^2	P
	N	(%)	N	(%)	N	(%)		
Blind eyes	287	(77.9)	191	(78.3)	96	(77.4)	0.05	0.8
End-stage	146	(39.7)	100	(40.9)	46	(37.1)	0.16	0.7
Mac scar	58	(15.8)	35	(14.3)	23	(18.5)	0.32	0.6
Cataract*	26	(7.1)	15	(6.15)	11	(8.9)	0.41	0.5
Optic atro**	14	(3.8)	9	(3.7)	5	(4.0)	0.09	0.7
Phthisis bulbi or enucleated	12	(3.26)	8	(3.3)	4	(3.2)	0.01	0.9
Ret detach	12	(326)	8	(3,3)	4	(3.2)	0.01	0.9
Others	19	(5.2)	16	(6.6)	3	(2.4)	0.84	0.3

End-stage: End-stage disease, Mac scar: Macular scar, Cataract*: With underlying pathology and no light perception, Optic atro**: Optic atrophy caused by other causes than end-stage disease or glaucoma, Ret detach: Retinal detachment

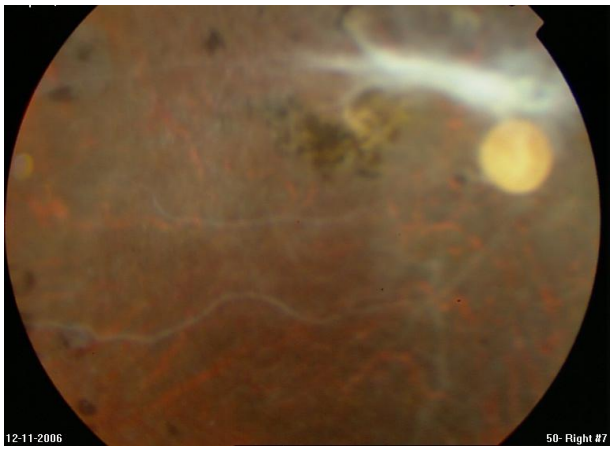

Figure 1. End-stage disease: retinal vascular necrosis or fibrosis, chorioretinal atrophy, optic atrophy

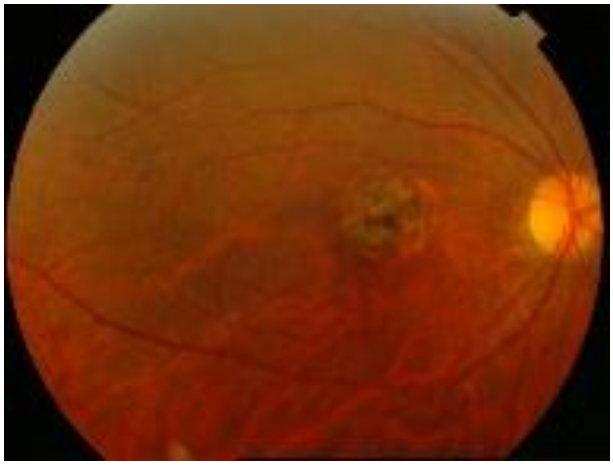

Figure 2. Macular scar and optic atrophy in ocular Behçet's Disease

Discussion

The ocular outcome of BD has been reported to be unfavorable. In a recent international survey of kitaichi et al,[16] data recruited from 15 BD centers, the final VA of 23% of cases was reported to be less than $^{20}/_{200}$. In the report of Zhang and coworkers[12] from China 20.4% of their 437 patients became blind, vision $^{1}/_{20}$ or less after mean follow-up of 47 months. However, in our registry of Shariati hospital of TUMS, a referral center for BD, in August 2008 among 6,021 registered BD patients only 267 (4.43%) of patients were legally blind (VA≤$^{1}/_{10}$). In one or both eyes after mean 10.9±7 years of follow-up.

Higher frequency of ocular BD in men has been reported by many authors,[9-13] but many investigators believe that the course of ocular BD is more severe in men and has a worst outcome in the male population.[10-13] In a retrospective report of Tugal-Tutkun et al[13] of 880 BD patients with uveitis the risk of visual loss after 5 years of treatment was estimated to be 21% for men vs. 10% of women. In the report of Bang et al[11] the risk of blindness after 5 years was calculated to be 29% for men vs. 6% for women and after 10 years was 65% vs. 33%, respectively. However, Davatchi et al[9,16] have indicated that the inflammatory indexes and the severity of ocular BD under treatment had the same outcome and improvement in two genders. We should keep in mind that the expression of the disease and the severity of BD could be different in diverse regions of the world.

Herein, we have presented 124 males and 63 females with BD, blind in one or both eyes at the last visit. We have focused on the ocular complications during the follow-up and finally we have indicated and compared the end-blinding manifestations in men and women.

In our patients the most frequent ocular manifestation was uveitis which was reported in 94.76% of the eyes, 93.77% of men and 96.72 % of women, P=0.5. Even though more frequent in women but statistically insignificant. Panuveitis was also more frequent in women 77.87% vs.71.78% of the eyes of men, P=0.55, statistically insignificant. In the investigation of Tugal-Tutkun[13] on ocular BD 60.2% of panuveitis has been reported 65.2% in men vs. 49.2% in women, P=0.0002, and inversely anterior uveitis has been observed more often in women 22.3% vs. 5.8% in men, P=0.0003. In our longitudinal investigation isolated anterior uveitis without involvement of vitreous was reported in 4.96% of the eyes, 4.25% of men and 6.56% of women, P=0.5. In the study of Yang[18] 75.9% of males vs. 49.8% of females had panuveitis and 3.3% of men vs. 16.7% of women had anterior uveitis which is in concordance with the report of Tugal-Tutkun.[13]

Our second most frequent ocular manifestation was retinal vasculitis observed directly by ophthalmoscopy. It was reported in 81.74% of the eyes of men and 77.87 % of women, P=0.6 (Table 4). In the report of Tugal-Tutkun[13] retinal vasculitis was observed in 89.0% of the eyes, 94.2% of men and 77.7% of women, P≤0.0001. Yang and coworkers[18] report 81.2% of retinal vasculitis observed by ophthalmoscopy and 97.9% of vascular leakage by fluorescein angiography.

In our report macular and paramacular scars were observed in 60.33% of the eyes 57.68% (N=139) of men versus 62.29% (N=76) of women. Total or partial optic atrophy was reported in 60.05% of the eyes, 61.4% (N=148) of men versus 57.4% (N=70) of women, but comparing two sexes none was statistically significant. Tugal-Tukun et al[13] report 19.4% (N=304) of macular dystrophy in their cases, 22% (N=237) of eyes of men vs.13.6% (N=67) eyes of women, P=0.000. In their report, macular edema was the most common complication which caused low vision which was observed in 44.5% (N=697) of eyes, 49.4% (N=532) of men and 33.5% (N=165) of women, P≤0.0001. Yang et al[18] report 38.2% of macular edema 43.5% in men and 24.5% in women, P=0,000. In our cases macular edema was observed in 58.4% (N=212) of eyes, 56.01 (N=135) eyes of men and 63.11% (N=77) eye of women, P=0.6.

Highly impaired vision at presentation has been considered a threatening sign in the outcome of the vision in BD.[11,13] Yang et al[18] report impaired vision of 0.05 or less in 36.3% (N=281) eyes of their patients at presentation. Tugal-Tutkun e al[13] report the initial VA of 0.1 or less in 30.9% of the eyes of men and 24.2% of women. In this present study 59.02% (n=144 eyes) of men and 68.55% (N=85 eyes) of women had severely impaired vision (VA=$^{1}/_{10}$ or less) at presentation which

could explain our very poor visual outcome in these particular BD patients. In a matched and controlled, investigation we have compared a group of blind BD patients with non-blind group. The blind group had significantly more impaired vision at presentation, P=0.000, and also all the ophthalmic manifestations and complications were significantly more frequent in that group.[19] Therefore, Severely impaired vision at presentation could be considered as an important risk factor in the outcome of the ocular disease. But we should keep in mind that in BD asymptomatic eyes with good vision could develop severe ocular lesions and become blind even under heavy treatment of BD, as it was noticed in some of our cases, and also it was shown that women responded better to the treatment of BD (Table 2). 47 eyes (19.3%) of men vs. 11 eyes (8.9%) of women lost their useful sight and became legally blind despite our heavy BD treatment indicating that women are better responder to BD treatment but the difference was not statistically significant (P=0.4).

In our patients only 6 cases (3.2%) had unilateral manifestations of ocular disease. In the report of Tugal-Tutkun et al[13] 21.9% and in the report of Yang and coworkers[18] 22.7% the ocular disease was unilateral. We believe that longer follow-up and meticulous ocular examination of the patients would reduce the number of unilateral ocular cases. In some publications all of the ocular cases have been reported to be bilateral.[20,21]

In our present investigation the most common cause of blindness was end-stage disease (Figure 1) (Table 5) which was observed in 39.67% (N=146) eyes, 40.98% (N=100) in men and 37.09% (N=46) in women, P=0.7. Although, it was more frequent in men but statistically it was insignificant. In the report of Tugal-Tutkun et al[13] this blinding cause is reported in 13% (N=204) eyes 14.9% (N=161) men and 8.7% (N=43) in women, P=0.000. The second blinding cause in our series was macular scar (Figure 2) which was registered in 15.76% (N=58) eyes, 14.34% (N=35) in men and 18.54% (N=23) in women, P=0.6. Even though more frequent in women but of no statistical significance. Pathologic cataract (caused by an underlying pathology and absence of light perception) was the cause of blindness in 6.15% (N=15) eyes of our men and in 8.87% (N=11) eyes of our women, P=0.5. Optic atrophy caused by optic neuritis, ischemic optic neuropathy (excluding end-stage disease and glaucoma) was reported in 3.69% (N=9) eyes in men and 4.03% (N=5) eyes in women, P=07. The other causes of blindness which were all more frequent in men were as follows: glaucoma 8 for I, cystoid macular edema 3 for 1, branch or central vein occlusion 3 for 1, and macular hole and vitreous hemorrhage one of each in men (Table 5).

Our study has many limitations. It is a retrospective report with all its pitfalls. In our investigation we have not presented a non-blind and matched, control group. We have compared a group of blind BD patients with probably more severe forms of the disease with cases of literature of less severity. However the force of this investigation is being a longitudinal one, covering almost thirty years of continuous and meticulous ocular investigation of BD patients.

Conclusion

At the last visit 78.28% (N=191) eyes in men and 77.42% (N=96) eyes in women had lost their useful sight, P=0.8. Although there was no discrepancy in the outcome of the vision in two genders, but the causes of blindness in men and women were somehow different, and the women responded better to the treatment. The most frequent cause of blindness in men was end-stage disease and macular scar was more frequent in women, but none were statistically significant.

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