Risk Factors of Blindness in Behcet’s Disease

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Abstract

**Purpose:** To investigate long-term ocular manifestations of oculocutaneous Behcet’s disease (BD), and the causes for blindness.

**Methods:** In August 2008, at Shariati hospital of Tehran (Behcet unit) all files of the ocular BD patients from 1976 to 2008 who were legally blind (Visual acuity = 20/200 or less) at least in one eye at the last visit and had at least three years of follow-up were reviewed and the desired informations were extracted. In this retrospective, comparative, investigation, 187 patients (374 eyes) were included in this group (Group 1). They were compared with 81 nonblind (at the last visit) ocular BD patients (162 eyes) who were visited and consequently selected in 2008, our control group (Group 2). They were matched in term of the duration of BD, approximately 18 years. All patients had conventional treatments for ocular BD.

**Results:** 65.2% (N=122) of the blind group were males vs. 56.8% (N=46) of the nonblind (control group), $X^2=1.73, P=0.189$. High number of initially impaired vision at presentation (vision of 20/200 or less) in the blind group; 230 eyes (61.5%) vs. 18 eyes (11.2%) in the control group was highly significant, $X^2=115.6, P=0.000$. More frequent cases of visible retinal vasculitis (by ophthalmoscopy) in the blind group; 290 eyes (77.5%) vs. 107 eyes (66.5%) in the control group, $X^2=7.78, P=0.005$, and higher frequency of vitritis and/or anterior uveitis 90.9% (N=340 eyes) vs. 75.3% (N=122 eyes) in the control group, $X^2=23.01, P=0.000$ were both considered two major blinding risk factors in ocular BD. At the last visit 77.3% (N=289) eyes in the main group were blind and the main cause of blindness was end-stage disease (retinal vascular necrosis and consequently chorioretinal atrophy and optic atrophy) in 38.5% (144 eyes), and the second major blinding cause was macular scar ± optic atrophy in 14.9% (N=56 eyes).

**Conclusion:** Although ocular BD can have a very severe and blinding outcome, early detection and prompt and intensive treatments may control the disease and save the sight.

**Keywords:** Ocular Behcet’s Disease, Blindness, Risk Factors

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Introduction

Behcet's disease (BD) is a chronic inflammatory vasculitis with remissions and recurrences. It is a vasculitis causing obliteration and necrosis of the vessels of nearly all organs. The disease is particularly propagated along the Silk Road, Far East, Middle East, Mediterranean territory and North Africa. The prevalence of the disease is variable in these regions 68, 13.2, and 80 to 370 per thousand thousand persons in Iran Japan and Turkey respectively. Etiology and pathogenesis of the disease is unclear. The diagnosis is done mainly by the clinical manifestations. The major criteria of the disease which are oral and genital aphthosis, skin lesions and ocular lesions (uveitis, retinal vasculitis) and along the minor criteria of BD which are vascular, gastrointestinal, neurologic, pulmonary etc. HLAB-51 typing, skin pathergy tests are helpful in diagnosis of BD but are not pathogonomic of the disease.

The rate of the ocular BD is reported to be variable in different countries and it has been reported to be 55.9% in Iran, 69% in Japan, 47% in Turkey and 34.8% in China. The ocular disease has been considered of a poor prognosis and about a quarter of the ocular BD patients becoming blind after few years of follow-up and treatment. However, in the registry of Shariati hospital of Tehran which is a referral center for BD, in the survey of August 2008 among 6021 BD patients only 4.43% of patients (N=267) were legally blind (vision= 20/200 or less), at least in one eye, after 10.9±7.8 years of the evolution of BD.

This is a long-term investigation of 187 cases (374 eyes) who were blind at least in one eye at the last visit and 81 BD patients (162 eyes) who were not blind at the final visit. In this controlled and matched investigation we have tempted to find out the complications, risk factors and causes of blindness in ocular BD.

Methods

In this retrospective and matched investigation 187 cases (374 eyes) of legally blind (Visual acuity= 20/200 or less) at the last visit (102 cases bilateral and 85 cases unilateral) are compared with 81 nonblind BD cases (162 eyes) (control group). In August 2008, at Shariati hospital of Tehran (Behcet unit) all the files of ocular BD patients from 1976 to 2008 who were legally blind at the last visit (Having visual acuity of 20/200 or less, at least in one eye) and having at least three years of follow-up were reviewed and the desired informations were extracted. 187 patients (374 eyes) were included in this group (Group 1). They were compared with 81 BD cases (162 eyes), nonblind at the final visit (Control group). The control cases were selected consequently at their last visit in 2008, matched in term of the duration of disease (The interval between the first manifestations of BD up to 2008). All the blind cases with less than three years of follow-up in our BD unit were excluded (N=80). All the included patients were the regular consultants of our multidisciplinary Behcet's clinic of Shariati hospital of Tehran University of Medical Sciences. The patients have had a regular ophthalmic and general examination at least twice yearly. The ophthalmic records had been registered on a previously prepared consultant sheet which includes all the required ocular informations. The visual acuity was taken by Snellen-chart and transformed to logMAR to calculate the means. The eyes were examined by Haag-Streit biomicroscopy. Three mirror of Goldmann or indirect ophthamoscopy was used to evaluate the fundi. Fluorescein-angiography, sonography and in the recent years optical coherence tomography were used in some selected cases.

The diagnosis of BD was done by the classification tree of BD confirmed by the International Study Group Criteria for BD. In all cases corticosteroids were administered orally at an initial dose of 0.5 mg/kg per day, followed by a gradual tapering. Immunosuppressor and/or immunomediator drugs were also used at the same time.

The duration of diagnosis of BD is calculated from the time of diagnosis of BD up to 2008. The duration of follow-up is calculated from the first to the last visit in our clinic. The delay in diagnosis of BD is defined the interval between the onset of the first symptom of BD and the time of diagnosis. The delay in diagnosis of ocular Behcet is considered the interval between the onset of the first ocular symptom (Claimed by the patients) and the first consultation and diagnosis of the ocular disease.
The term retinal vasculitis has been used when sheathing of the retinal vessels, obliteration, fibrosis or necrosis of vessels has been observed by ophthalmoscopy, excluding imaging on fluorescein-angiography. In the blind group seven patients had apparently unilateral involvement of the eye. In the control group in two patients the ocular BD was unilateral. Data were analysed using $\chi^2$ and one way ANOVA tests with SPSS V.11, P-value of 0.05 or less was considered significant.

**Results**

Eventually 187 blind (vision=$20/200$ or less) cases (102 bilaterally, and 85 cases unilaterally blind) have been compared with 81 nonblind (At the last visit) of ocular BD cases. 65.2% (N=122) of the blind group vs. 56.9% (N=46) of the control group were males, $\chi^2=21.73$, P=0.189.

As it is indicated in table 1, the mean age of the blind group at presentation was 32.1±9.2 years (Range 8 to 55 years) and that of the control group was 33.7±9.5 years (Range 7 to 55 years).

The delay in ocular diagnosis and treatment in 174 cases of the blind group was 2.6±2.8 years (13 patients got the eyes involved during the follow-up). In the control group the delay in ocular diagnosis and treatment in 49 cases was 2.35±2.38 years (32 cases got the eyes involved during the follow-up). The number of the cases who had late involvement of the eyes and received immediate and intensive treatment for their ocular BD was significantly higher in the control group, $\chi^2=38.95$, P=0.000.

In the blind group 61.5% (N=230 eyes) had vision of $20/200$ or less at presentation vs. 11.1% (N=18 eyes) in the control group, $\chi^2=115.6$, P=0.000.

The initial and final mean vision of the blind group were $1.24±1.02$ logMAR and $2.0±1.4$ logMAR, and that of the control group were $0.27±0.45$ logMAR and $0.2±0.21$ logMAR, respectively. Indicating a very high rate of visual impairment in the initial and final vision of the blind group.

The delay in diagnosis of BD, the duration of diagnosis and follow-up of the two groups are indicated in table 1. The mean duration of BD in both groups was approximately 18 years.

The frequency of 77.5% visible retinal vasculitis in the blind group was significantly higher than the frequency of 66% in the control group ($\chi^2=7.78$, P=0.005) (Table 2). A significantly greater proportion of cases had anterior uveitis and/or vitritis in the blind group compared with cases of the control group (90.9% vs. 75.3%; P<0.001). The mean duration of visible retinal vasculitis in the blind and control groups were 5.9±5.9 and 4.7±6.4 years respectively. This difference was not statistically significant (P=0.08).

The ocular manifestations of the disease during the follow-up in the blind group and control group are indicated in table 2. Macular or paramacular scar, partial or total optic atrophy are significantly more frequently seen in the blind group, $\chi^2=120.5$, P=0.000 and $\chi^2=113.75$, P=0.000, respectively. Macular edema was significantly more frequent in the control group 66.7% (N=108 eyes) vs. 56.7% (N=212 eyes), $\chi^2=4.68$, P=0.03.

At the last visit 77.3% (N=289 eyes) in the main group were legally blind (102 bilateral, 85 unilateral).

The main causes of blindness were end-stage disease (Retinal vascular necrosis or fibrosis and consequently chorioretinal atrophy and optic nerve atrophy) (Figure 1) which was observed in 38.5% (N=144) eyes, macular scar±optic atrophy in 14.9% (N=56 eyes), Pathologic cataract (Poor or no light perception) 6.4% (N=24 eyes), optic atrophy 4.3% (N=16 eyes), phthisis bulbi 3.74% (N=14 eyes), retinal detachment 3.2% (N=12 eyes), glaucoma 2.7% (N=10 eyes), etc (Table 3).
Figure 1. End-stage Behcet’s disease optic atrophy macular scar

Table 1. Characteristics of 187 blind BD patients compared with 81 nonblind BD patients

<table>
<thead>
<tr>
<th></th>
<th>Blind group</th>
<th>Control group</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>32.1±9.2</td>
<td>33.7±9.5</td>
<td>133</td>
<td>0.41</td>
</tr>
<tr>
<td>Male cases (%) (N=122)</td>
<td>65.2%</td>
<td>56.8% (N=46)</td>
<td>χ²=1.73</td>
<td>0.189</td>
</tr>
<tr>
<td>Impaired vision (%) (230 eyes)</td>
<td>61.5%</td>
<td>11.1% (18 eyes)</td>
<td>χ²=115.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Delay in diag. BD (years)</td>
<td>4.9±4.5</td>
<td>5.2±4.24</td>
<td>0.517</td>
<td>0.60</td>
</tr>
<tr>
<td>Duration of diagnosis (years)</td>
<td>14.2±6.4</td>
<td>12.7±6.01</td>
<td>1.94</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of follow-up (years)</td>
<td>10.4±6.4</td>
<td>11.3±5.9</td>
<td>1.17</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Mean age: Mean age at presentation
Impaired vision: 20/200 or less at presentation
Delay in diag. BD: Delay in diagnosis of Behcet disease
Duration of diagnosis: Interval between diagnosis and 2008
Duration of follow-up: First to last consultation

Table 2. Comparison of ocular lesions during the follow-up between the blind groups, 187 cases (374 eyes) and control group, 81 cases (162 eyes)

<table>
<thead>
<tr>
<th></th>
<th>Blind group</th>
<th>Control group</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflam cells (%) N eyes</td>
<td>340</td>
<td>122</td>
<td>23.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Retinal vasculitis (%) N eyes</td>
<td>290</td>
<td>107</td>
<td>7.78</td>
<td>0.005</td>
</tr>
<tr>
<td>Macular scar (%) N eyes</td>
<td>219</td>
<td>12</td>
<td>120.53</td>
<td>0.000</td>
</tr>
<tr>
<td>Optic atrophy (%) N eyes</td>
<td>218</td>
<td>14</td>
<td>113.75</td>
<td>0.000</td>
</tr>
<tr>
<td>Macular edema (%) N eyes</td>
<td>212</td>
<td>108</td>
<td>6.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Disc edema (%) N eyes</td>
<td>132</td>
<td>79</td>
<td>8.50</td>
<td>0.004</td>
</tr>
<tr>
<td>Cataract (%) N eyes</td>
<td>282</td>
<td>93</td>
<td>4.46</td>
<td>0.03</td>
</tr>
<tr>
<td>Glaucoma (%) N eyes</td>
<td>14</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phthisis bulbi (%) N eyes</td>
<td>14</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal detachment (%) N eyes</td>
<td>12</td>
<td>1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Retinal vessel occlusion (%) N eyes</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinitis (%) N eyes</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuritis (%) N eyes</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous hemorrhage (%) N eyes</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inflam cells: Inflammatory cells indicating anterior uveitis or vitritis or both
Retinal vasculitis: Periartritis, periphlebitis, vascular necrosis
Macular scar: Macular or paramacular scar
Optic atrophy: Partial or total optic atrophy
Table 3. End blinding results in our main group 187 patients (374 eyes)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N eyes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legally blind</td>
<td>289</td>
<td>77.3</td>
</tr>
<tr>
<td>End-stage disease</td>
<td>144</td>
<td>38.5</td>
</tr>
<tr>
<td>Macular scar/toxic atrophy</td>
<td>56</td>
<td>14.9</td>
</tr>
<tr>
<td>Pathologic cataract</td>
<td>24</td>
<td>6.4</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>16</td>
<td>4.3</td>
</tr>
<tr>
<td>Phthisis bulbi</td>
<td>14</td>
<td>3.7</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>12</td>
<td>3.2</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>10</td>
<td>2.7</td>
</tr>
<tr>
<td>CME</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>CRVO, BRVO</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Macular hole</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

End-stage disease: Retinal vascular necrosis, chorioretinal atrophy, optic Atrophy
Pathologic cataract: Cataract with no or poor light perception with underlying unknown pathology
CME: Cystoids macular edema
CRVO, BRVO: Central or branch retinal vein occlusion

Discussion

It has been reported that the visual outcome of ocular BD is unfavorable. In a recent international investigation of 25 BD centers which included 1465 ocular BD patients the final visual acuity of 23% of the cases was reported to be less than $1/10$. In a report from China, 20.4% of their 437 patients became legally blind and they estimated that the risk of blindness after 10 years of follow-up and treatment was 62.2%. However, in our registry of Shariati hospital in Tehran, a tertiary referral center for BD, in August 2008 among 6,021 BD patients only 4.43% were registered to be legally blind, in one or both eyes (Vision=<20/200 or less), after 10.9±7.8 years of the course of BD. Although, the ocular BD can be sight-threatening by its undesirable evolution and its complications such as optic atrophy, retinal vascular thrombosis, necrosis, fibrosis and chorioretinal atrophy, these complications in most cases may be prevented by a prompt aggressive treatment of the ocular disease.

Higher frequency of ocular BD in male population has been indicated by many authors. In the report of Davatchi et al of 4,717 patients 62% of men vs. 49% of women presented ocular BD. The difference was highly significant, $x^2=105.95$, P=0.000. In the report of Hamzaoui et al 32.2% (N=167) of the BD patients had ocular involvement (37.5% of men and 17.9% of women). In this present work the predominance of male cases with ocular BD has been shown in both blind and control groups.

Many authors believe that not only men are more predisposed to have ocular BD but also the course of the ocular disease is more severe in the male population. However, Davatchi et al have shown that the inflammatory indices and the severity of ocular BD had the same outcome and improvement under treatment in two sexes.

Herein we have presented the ocular symptoms and complications of ocular BD patients and the risk factors and causes of blindness in our patients. In this investigation impaired visual acuity at presentation 61.5% (N=230 eyes) in the blind group vs. 11.1% (N=18 eyes) in the control group was of high significance in the blinding outcome of the disease=$0.000$. Yang et al reported impaired vision of 0.05 or less in 36.3% (N=281 eyes) of their cases at first examination. In the report of Tugal-Tutkun et al the visual acuity of 0.1 or less at presentation was reported in 30.9% of the eyes in males and 24.2% in females.

In this investigation, although the ocular outcome of our main group was very poor but on the contrary in our control group the end-results have been very satisfactory which could be explained by their initial good vision
in 88.8% (N=144) of the eyes, and in many cases a prompt and intensive treatment for their ocular BD.

In our cases only 7 patients (1.87%) in group 1 and 2 patients (1.23%) in control group had apparently unilateral ocular BD. This could be explained by our close, careful and long-term follow-up of the patients to detect small and transient symptoms such as peripheral and central retinal vasculitis, macular and disc edema, etc. In the report of Tugal-Tutkun\textsuperscript{17} 21.9% and in the report of Yang\textsuperscript{19} 22.7% of their cases were unilateral.

In this report we have shown that the visible retinal vasculitis (Periphelebitis, periarteritis, vascular fibrosis or necrosis or occlusion) was significantly more frequent in the blind group, compared with the control group (P<0.001). Retinal vasculitis seen on fluorescein-angiography and leakage of dye has not been considered in our study. As it has been shown by Yang et al\textsuperscript{19} that dye leakage from the retinal vessels can be seen in almost all ocular BD cases (97.9%).

The higher frequency of anterior uveitis and/or vitritis (Table 2) in our main group compared with the control group (P<0.001) was considered as another blinding risk factor in the outcome of the ocular disease.

Cataract was seen in 75.4% (N=282 eyes) of our group 1 vs. 57.4 % (N=93 eyes) in the control group (\(\chi^2=4.46, P=0.03\)), which could be explained by the severity of the ocular disease and longer corticosteroid therapy in that group. At the end of our investigation pathologic cataract (Poor or no light perception) was the cause of blindness in 6.4% (N=24) of the patients. The pathogenesis of these cataracts was due to the underlying nonrecognized causes.

Macular edema is reported only in 56.7% (N=212 eyes) of the blind group vs. 66.7% (N=108 eyes) of the control group. The difference can be explained by existence of advanced and irreversible macular lesions and scarring at the initial visit in our main group. In the investigation of Tugal-Tutkun et al\textsuperscript{17} macular edema was the most common complication and was observed in 44.5% (N=697 eyes). Yang et al report 38.2% of macular edema in their ocular BD patients\textsuperscript{19}.

In our main group the most evident cause for blindness was the end-stage disease (38.5%, 144 eyes) which was caused essentially by the necrosis or fibrosis of the retinal vessels and consequently chorioretinal and optic atrophy. In the report of Tugal-Tutkun et al\textsuperscript{17} this complication is reported in 13% (204 eyes). The second blinding complication in our series was macular scar±optic atrophy which was noticed in 14.9% (56 eyes). Optic atrophy in these cases was caused by optic neuritis or ischemic optic neuropathy. In the report of Tugal-Tutkun et al\textsuperscript{17} macular degeneration is reported in 19.4% (304 eyes) of the eyes.

Although the end ocular result was satisfactory in our control group but we can postulate that they had a less aggressive disease and we should emphasize that at presentation the disease had less progression, they had better visual acuities and in many cases were treated promptly and aggressively.

\section*{Conclusion}

In our investigation one of the most important risk factors for blindness was initially impaired vision caused by the aggressive and destructive ocular lesions. Rapid recognition of the ocular disease and prompt and aggressive treatment of ocular BD can save many sights.

\section*{Acknowledgment}

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\section*{References}