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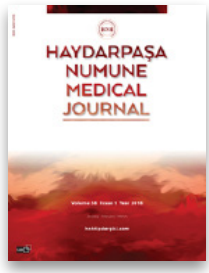

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ORIGINAL ARTICLE

Long Term Visual Outcomes of Uveitis Associated with Behcet's Disease

Selim Bölükbaşı[1], Yılmaz Özyazgan[2]

[1]Department of Ophthalmology, University of Health Sciences Turkey, Okmeydani Health Aplication and Research Center, Istanbul, Turkey
[2]Department of Ophthalmology, Dunya Goz Hospital, Istanbul, Turkey

Abstract

Introduction: To compare the visual prognosis of patients with Behcet's uveitis who presented after 1977-1987 and 2000-2010.

Methods: In this observational, retrospective study, 382 eyes of the 200 patients (48 female and 152 male) were included. Patients who visited the clinic between 1977 and 1987 were classified into Group 1, and patients who visited between 2000 and 2010 into Group 2. Group 1 consisted of 194 eyes (100 patients), and Group 2 consisted of 188 eyes (100 patients). Best corrected visual acuity (BCVA) measurements, biomicroscopic and fundoscopic examinations, gender, age of onset of uveitis, numbers of ocular attacks per year from the onset of ocular disease, immunosuppressive drugs and ocular complications were noted by medical records. Grade of uveitis was noted at the first and last visit.

Results: In this study, 76% of the patients were male and 24% of the patients were female. Bilateral ocular involvement was in 91%. The mean age of onset of uveitis was 29 years. Mean ocular attack number was 4.21 in Group 1 and 3.25 in Group 2. Kaplan Meier survival analysis estimated the risk of losing useful vision (BCVA>0.1) at the last visit for Group 1 and Group 2 as 64.50% and 48.81% (Log Rank: 11.44, $p<0.001$). Mean last visit grade was 3.24 in Group 1 and 2.47 in Group 2 ($p<0.001$). Mean last BCVA was 0.41 in Group 1 and 0.65 in Group 2 ($p<0.001$).

Discussion and Conclusion: There was a trend for a better visual prognosis in patients who presented after 2000 due to following-up ocular attacks closer and using azathioprine, cyclosporin A and new treatment agents for severe posterior uveitis.

Keywords: Behcet's disease; ocular attack; uveitis; visual acuity.

Behcet's disease (BD) is a chronic relapsing vasculitis with unkown etiology and may affect many systems in the same or different time of periods. BD may affect almost all vascularized systems and result in complications associated with occlusive vasculitis[1]. Immunological mechanisms and infectious agents are held responsible for the genetic predisposition in the pathogenesis of this multifactorial disease[2].

The most severe symptoms of the disease occur in the eye. Loss of vision develops 3-10 years after the onset of oral or genital ulcerations, especially in the first year in the vast majority of patients[3–6]. The visual prognosis depends on the frequency and severity of the uveitis attacks, the length of the interval between the attacks and the involvement of the anterior or posterior segment of the eye. In some patients, attacks are limited to the anterior segment and visual prognosis tend to be better, and these patients are generally female[7]. However, patients with posterior segment involvement are not so lucky, and they may experience visual loss in the time of periods that mentioned above. Re-

Correspondence (İletişim): Selim Bölükbaşı, M.D. Saglik Bilimleri Universitesi, Okmeydani Saglik Uygulama ve Arastırma Merkezi, Istanbul, Turkey
Phone (Telefon): +90 532 700 79 39 **E-mail (E-posta):** selimbolukbasi@hotmail.com
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peated attacks result in serious complications in the eye, such as cataract, secondary glaucoma, macular degeneration, macular hole, cystoid macular edema, optic atrophy, retinal detachment and phthisis bulbi[8].

In this study, we aimed to compare the visual prognosis of two groups and examine the factors affecting them by retrospectively in the patients that were followed-up with uveitis associated with BD whose first application dates were 1977-1987 (Group 1) and 2000-2010 (Group 2) in the Department of Uveitis and BD of Cerrahpasa Medical School.

Materials and Methods

In this retrospective, observational study, medical records of patients with a diagnosis of uveitis associated with BD, who were followed-up at Cerrahpasa Medical School Uvea-Behcet Department, were reviewed. The patients whose first application dates were 1977-1987 and 2000-2010 were classified as Group 1 and Group 2, respectively. All patients had been consulted with rheumatology and dermatology departments.

Complete ophthalmic examinations, including the measurements of the BCVA using Snellen charts, slit-lamp biomicroscopy and dilated fundus examination findings, were noted retrospectively for every visit.

Each patient's attack number and intervals of attacks, ocular findings and complications, anti-inflammatory and immunosuppressive drug treatments, damage grading at the beginning and end of the follow-up time were noted.

Patients who were followed up regularly for at least 48 months were included in this study.

The damage classification was made according to the following scale:

Grade 0: No eye involvement

Grade 1: Eye involvement (+) (anterior segment sequela and/or vitreous opacity) but retinal involvement (-)

Grade 2: Anterior segment sequela, vitreous opacity, cystoid macular edema, peripheral venous sheathing

Grade 3: Mild optic atrophy, diffuse venous sheathing, minimal pigmentary changes in outside and inside of the arcade

Grade 4: Manifest optic atrophy and vaso-occlusive changes, diffuse venous sheathing, diffuse pigmentary changes in outside and inside of the arcade

Grade 5: Total optic atrophy, advanced grade vaso-occlusive changes, excessive pigmentary changes, especially visual acuity is a light perception or absolute

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics. The variables were investigated using histograms and analytical methods to find out whether or not they are normally distributed. Paired Samples t-test and repeated measures ANOVA were used to compare variables between the groups. A p-value less than 0.05 ($p<0.05$) and 0.01 ($p<0.01$) were considered statistically significant and highly significant, respectively. Correlation between the attack number of uveitis and BCVA were evaluated with scatter plot analysis. Visual acuity above 0.1 was considered a useful vision. Two groups were compared with the Kaplan-Meier survival analysis method by selecting those with visual acuity above 0.1.

Results

In the study, 382 eyes of 200 patients were included (48 female and 152 male). Patients who visited the clinic between 1977 and 1987 were classified into Group 1, and patients who visited between 2000 and 2010 into Group 2. Group 1 consisted of 194 eyes (100 patients) and Group 2 consisted of 188 eyes (100 patients).

There were 26 female, 74 male patients in Group 1 and the mean age at onset of uveitis was 30 years (range, 15 to 49 years). There were 22 female, 78 male patients in Group 2 and the mean age at onset of uveitis was 28 years (range, 14 to 57 years). Male/Female ratio was 2.8:1 in Group 1, 3.5:1 in Group 2 and 3.1:1 in all of the patients.

Ocular involvement was bilateral in 182 patients (91%) and unilateral in 18 patients (9%). Ocular involvement was bilateral in 94 (94%) and 88 (88%) patients in Group 1 and Group 2, respectively.

In this study, 19 (9.5%) patients had their first uveitis attack under the age of 20. One hundred seventy-eight patients (89%) were diagnosed onset of uveitis in between 20-50 years. There was not any statistical difference between the two groups ($p>0.05$).

At the end of the 1st, 2nd, 3rd, 4th year and after the 4th year

Table 1. Mean attack numbers by years in Group 1 and Group 2

Attack (year)	Group 1	Group 2
Mean Attack	4.21	3.25
Attack 1st year	0.95	1.47
Attack 2nd year	0.32	0.50
Attack 3rd year	0.27	0.27
Attack 4th year	0.28	0.19
Attack after 4th year	2.34	0.81

mean attack numbers are shown in Table 1. While the mean attack number was 4.21 in Group 1, it was 3.25 in Group 2 (p=0.07). The mean attack number at the end of the 1st and 2nd year was higher in the 2nd Group (p<0.05), but after the 4th year, it was higher in the 1st Group (p<0.001).

Papil edema occurred in 22 (5.7%) patients (7 patients (3.6%) in Group 1 and 15 patients (7.9%) in Group 2, p<0.05) in this period.

Branch retinal vein occlusion was diagnosed in 15 patients (%3.9) (3.7% in Group 1 and 4.4% in Group 2, p<0.05).

Systemic treatment modalities applied to Group 1 and Group 2 are shown in Table 2. While the percentage of steroid, azathioprine and cyclosporine using was higher in Group 2 (p<0.001), cyclophosphamide using was higher in Group 1 (p<0.001).

The first and last visit grade and BCVA (Snellen) of the patients are shown in Table 3. The mean last visit grade was 3.24 and 2.47 in Group 1 and Group 2, respectively (p<0.001). At the last visit, damage in Group 2 was statistically significantly higher. Mean last visit BCVA (Snellen) was 0.41 in Group 1 and it was 0.65 in Group 2 (p<0.001). BCVA was statistically significantly better in Group 2 at the end of the follow-up.

In the first visit, the number of eyes with BCVA greater than 0.1 was 169 in Group 1 and it was 188 in Group 2. At the end of the follow-up, the number of eyes that BCVA decreased lower than 0.1 was 109 eyes in Group 1 and 88 eyes in Group 2. Two groups were compared with the Kaplan-Meier Survival Analysis method. The risk of losing vision (BCVA <0.1) who were presented in 1980s and 2000s were 64.50% vs 48.81%, respectively (Log Rank: 11.44, p<0.001).

Figure 1 shows the correlation between the attack number of uveitis and BCVA. Statistically highly significant negative correlation was found between the attack number of uveitis and BCVA (r= -0.25, p<0.001).

Table 2. Systemic therapy in Behcet's uveitis

Systemic therapy	Systemic therapy in Behcet's uveitis			
	1980s		2000s	
	Patient n=100)	%	Patient (n=100)	%
Systemic steroid	41	41	69	69
Azathioprine	34	34	90	90
Cyclopsorine A	11	11	78	78
Colchicine	28	28	36	36
Cyclophosphamide	25	25	3	3
Interferon	2	2	35	35
Mycoohenolic Acid	0	0	4	4
Infliximab	0	0	5	5

Table 3. The first and last visit grade and best corrected visual acuity (BCVA) of the patients

Group	First Visit Grade	Last Visit Grade	First Visit BCVA	Last Visit BCVA
Group 1	1.64	3.24	0.62	0.41
Group 2	1.74	2.47	0.66	0.65

Discussion

The underlying pathology of BD is an occlusive and necrotizing vasculitis that can affect both arteries and veins in all systems[9]. Ocular involvement in BD is nearly 70%. Typical ocular involvement is uveitis with recurrent attacks. During these attacks, iritis, hypopyon, chorioretinitis, retinal vasculitis, retinal vein occlusion, optic neuritis, retinal neovascularization and vitreous hemorrhage can be seen. Less frequently observed nonspecific eye findings are conjunctivitis, conjunctival ulcer, keratitis, episcleritis, scleritis and extraocular muscle paralysis due to the neurological involvement of BD[10,11]. Intraocular inflammation reveals chronic relapsing bilateral non-granulomatous uveitis that may involve the anterior segment, the posterior segment

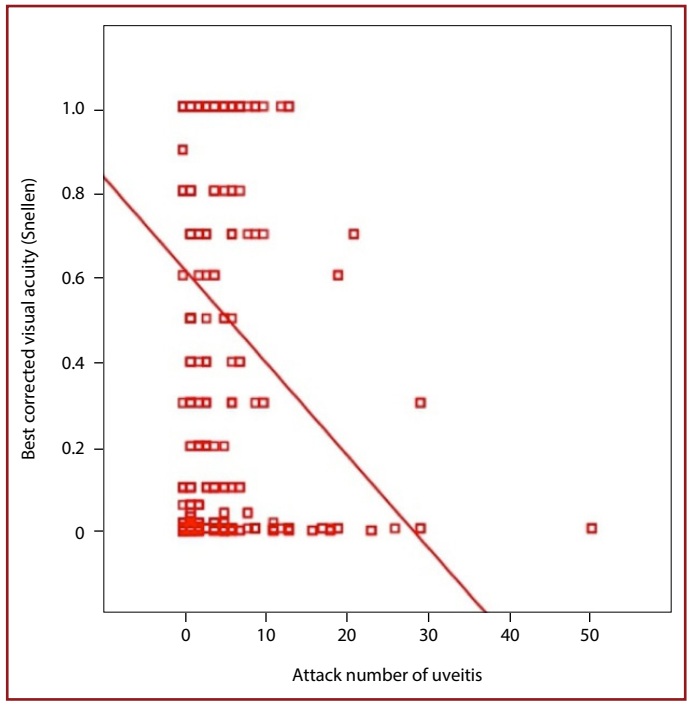

Figure 1. Correlation between attack number of uveitis and best corrected visual acuity.

or both (panuveitis)[12]. Type of uveitis is important concerning therapeutic and prognostic aspects. In patients with recurrent posterior segment involvement, uveitis causes significant vision loss[13].

Ocular involvement in BD is more frequent in males in the whole world. Male gender and disease in early ages are bad prognostic factors concerning loss of visual acuity[14,15]. In our study Male/Female ratio was 3.1:1. Two studies from Turkey reported this ratio lower (2.1:1)[16,17]. Other studies from different countries reported similar results like ours[18,19].

The frequency of bilateral involvement ranges from 78% to 95% in many reports; similarly it was 91% in our report[3,13,16,20,21].

When we compared two groups concerning hypopyon, hypopyon percentage was lower in Group 2. (Group 1: 14.4%, Group 2: 7.4%) In the 2000s, the development of hypopyon decreased statistically significantly. In all eyes, the percentage of hypopyon was 11%. Similarly, Tugal-Tutkun et al.[17] reported hypopyon development 12%.

Papilledema was noted in 3.6% of 194 eyes in Group 1 and 7.9% of 188 eyes in Group 2. There was no statistically significant difference between groups. In literature Khairallah et al. and Yang et al. observed papilledema in uveitis associated with BD 57.7% and 63.7% of eyes, respectively[22,19]. As similar to our report, Tugal-Tutkun et al. and Ouazzani et al. indicated papilledema in Behcet's uveitis 5.5% and 10% of eyes, respectively. We observed papilledema in 22 eyes (5.7%)[17,23].

Severity and number of attacks determine the visual prognosis due to irreversible damage in posterior segment[24]. When we compared the grades of damage at final visit, Grade 5 which is the worst stage was found 31.4% of eyes in Group1 and 9.6% of eyes in Group 2. There was highly statistically significant difference between the groups. Our data showed that uveitis associated with BD causes much more damage to the eyes of patients who were followed up in the 1980s. When we compared the grades of damage at first visit, Grade 5 was found 6.7% of eyes in Group 1 and 3.2% of eyes in Group 2. This might be related to the late diagnosis in the 1980s.

In a report, having lots of uveitis attack have been shown to be associated with poor prognosis[24]. After the 4th year, the mean attack number was statistically significantly higher in Group 1. When the groups were analyzed, it was seen that the mean number attacks per year decreased from the 1st year to the 4th year. After the 4th year, there was a remarkable increase in the average number of attacks in Group 1 and a slight increase in Group 2.

While there was no statistically significant difference between the two groups concerning baseline BCVA, there was statistically significant difference between the groups in terms of final BCVA and BCVA was almost preserved in Group 2. While there was no statistically significant difference between the two groups with respect to baseline damage grade, there was a statistically significant difference between groups regarding final damage grade. Based on these findings, it was clear that the prognosis was better in Group 2.

We have indicated that the risk of losing vision (BCVA <0.1) who were presented in the 1980s and 2000s was 64.50% vs. 48.81%, respectively (p<0.001). There was a highly statistically significant difference between groups. Tutkal-Tugun et al.[17] demonstrated that the risk of losing vision in seven years for male patients who were diagnosed 1980s and 1990s were %30 vs. %21, respectively. Ben Ezra et al.[5] have reported that 74% of eyes lost useful visual acuity in ten years.

Different treatment combinations have been used for uveitis associated with BD. Although conventional medicines like colchicine, corticosteroids, cyclophosphamide and chlorambucil are used to suppress ocular inflammation, their effectiveness may not be enough in serious cases[24–28]. Cyclosporin A and azathioprine came into use immunosuppressive agents after 1985 and 1990, respectively. Tugal-Tutkun et al.[17] have showed that eyes with uveitis associated with BD had better visual results in the 1990s then 1980s, and they attributed this to the more aggressive treatment and effectiveness of cyclosporine A. In another publication from Taiwan, they stated that low-dose steroid combined with cyclosporine A could be used for the patients with posterior segment involvement and repeated recurrences. If this combination was not sufficiently effective to prevent recurrence, they suggest to adding azathioprine, methotrexate and other immunosuppressive treatment agents[29]. In our study, we indicated that azathioprine (90%) and cyclosporine (78%) were used much more frequent in the 2000s when the visual prognosis was clearly better. Also, it has been shown that the visual prognosis would be better with the widespread use of new immunomodulators and biological agents like infliximab and adalimumab[30].

Conclusion

Basically, severity and number of repeated attacks determine the visual prognosis in Behcet's uveitis. We have demonstrated that there was a trend for a better visual prognosis in

patients who presented after 2000 due to following-up ocular attacks closer, more aggressive treatment combinations in difficult cases, using azathioprine, cyclosporin A and new treatment agents for severe posterior uveitis.

Ethical Committee Approval: The Ethics Committee of Istanbul University Cerrahpasa Medical Faculty provided the ethics committee approval for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.B., Y.O.; Design: S.B., Y.O.; Data Collection or Processing: S.B.; Analysis or Interpretation: S.B., Y.O.; Literature Search: S.B.; Writing: S.B.

Conflict of Interest: None declared.

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