Clinical Findings Ocular Involvement in Behçet's Disease

Behçet Hastalığının Göz Tutulumunda Klinik Bulgular

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ABSTRACT Objective: To report the demographic and clinical characteristics of ocular Behçet's disease (BD) patients from Mediterranean region of Turkey. **Material and Methods:** In this retrospective study, we reviewed the clinical results of 249 patients with BD, examined in the Uveitis and Behçet Clinic of Ophthalmology Department, Akdeniz University School of Medicine, between 1988 and 2009. The mean follow-up period was 61.7±50 (6-252) months. Age at the onset of disease, sex, extraocular and ocular findings, ocular complications, final visual acuity and choice of treatment were recorded. **Results:** Among 249 patients, 180 (72.3%) had ocular involvement, 147 (81.7%) being bilateral. The male/female ratio of ocular involvement was 2.1:1. Male patients had a significantly higher ratio of involvement ($p<0.001$). The median age at onset of BD was 29 (11-60) years, with no difference between sexes ($p=0.861$). The most common ocular finding was vitritis, observed in 225 (68.8%) eyes. Epiretinal membrane, cataract and chronic cystoid macular edema were the most common ocular complications found in 98 (30%), 95 (29.1%), and 93 eyes (28.4%), respectively. The final visual acuity was 0.05 or worse in 86 (26.3%), and 0.5 or better in 209 eyes (63.9%). Male patients ended up with a lower final visual acuity when compared to the female patients ($p=0.008$). **Conclusion:** Ocular BD still remains a blinding disease, functional vision loss occurring in one-quarter of the eyes. The male patients have more frequent and severe ocular involvement with no difference regarding the age at onset of BD.

Key Words: Behcet syndrome; uveitis; uveitis, posterior

ÖZET Amaç: Türkiye'nin Akdeniz Bölgesi'nde, Behçet hastalığı (BH) göz tutulumu olan hastaların demografik ve klinik özelliklerini bildirmek. **Gereç ve Yöntemler:** Bu retrospektif çalışmada, Akdeniz Üniversitesi Tıp Fakültesi Göz Hastalıkları Anabilim Dalı Uvea ve Behçet Birimi'nde 1988 ile 2009 arasında izlediğimiz 249 Behçet hastasının klinik bulgularını derledik. Ortalama takip süresi 61,7±50 (6-252) ay idi. Hastalığın başlangıç yaşı, hastaların cinsiyeti, klinik bulguları, göz komplikasyonları, son görme keskinliği ve tedavi tercihi kaydedildi. **Bulgular:** Göz tutulumu, 249 hastanın 180'inde (%72,3) saptandı; 147 (%81,7) hastada her iki göz tutulmuştu. Göz tutulumu görülenlerde erkek/kadın oranı 2,1:1 idi. Erkek hastalarda anlamlı olarak yüksek göz tutulum oranı izlendi ($p<0,001$). BH başlangıç yaşı ortanca 29 (11-60) iken, cinsiyet farkı izlenmedi ($p=0,8$). En sık göz bulgusu 225 (%68,8) gözde görülen vitrit idi. Epiretinal membran, katarakt ve kronik kistoid maküla ödemi en sık görülen komplikasyonlar iken, sırasıyla 98 (%30), 95 (%29,1), ve 93 (%28,4) gözde izlendi. Nihai görme keskinliği 86 (%26,3) gözde 0,05 veya daha kötü, 209 (%63,9) gözde ise 0,5 veya daha iyi seviyedeydi. Erkek hastaların son muayenedeki görme keskinliği kadın hastalardan daha kötüydü ($p=0,008$). **Sonuç:** Oküler BH, hastaların dörtte birinde fonksiyonel görme kaybı görülen, kör edici bir hastalık olmaya devam etmektedir. Erkek hastalarda daha sık ve daha ağır göz tutulumu görülürken, göz tutulum yaşında cinsiyetler arası fark yoktur.

Anahtar Kelimeler: Behçet sendromu; üveit; üveiat, posterior

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Behçet's disease (BD) is an inflammatory, multisystem vasculitis of unknown etiology, first described in 1937 by Turkish dermatologist, Dr. Hulusi Behçet. The disease is characterized by recurrent oral aphtous ulcers, genital ulcerations, skin lesions and uveitis.[1,2] Gastrointestinal tract and central nervous system involvement are less frequent, but can be fatal.[3] BD affects mainly people living around the ancient Silk Road, which extends from eastern Asia to the Mediterranean Basin; Turkey having the highest prevalence.[2-4]

Ocular lesions, which occur in 60-80% of patients, is characterized by posterior or panuveitis with occlusive retinal vasculitis, and can cause severe reductions in visual acuity, and even blindness.[5,6] Along with central nervous system involvement, eye involvement is the most severe manifestation of BD. Ocular involvement in BD is associated with legal blindness in more than half of the patients.[5,6] In the present study, we examined the demographical aspects, clinical and ocular manifestations, ocular complications and treatment of ocular BD in patients who live in the Mediterranean region of Turkey.

MATERIAL AND METHODS

We retrospectively analyzed the medical data of 249 BD patients examined in Uveitis and Behçet Clinic of Department of Ophthalmology, Akdeniz University School of Medicine, between 1988 and 2009. The median of follow-up period was 61.7±50 (6-252) months with a median of 44 months. All patients were Caucasians from the Mediterrenean Region of Turkey. All patients fulfilled the criteria of the International Study Group for Behçet's Disease.[7] The study adhered to the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee of Akdeniz University School of Medicine.

We obtained a detailed medical history from each patient at first visit, focusing on systemic and ocular symptoms and findings of BD. We performed a complete ophthalmologic examination at each visit, which includes a Snellen best corrected visual acuity, applanation tonometry, slit lamp biomicroscopy and indirect ophthalmoscopy.

We analyzed the demographic data (sex of patient, age at onset of ocular involvement), extraocular systemic manifestations of BD, pathergy test results, and ocular manifestations (including laterality, type of uveitis, ocular complications), and the type of treatment administered.

We diagnosed retinal vasculitis depending on either observation of inflammatory sheathing and gliosis of the vessels on ophthalmoscopy, or fluorescein leakage and staining of the vessels on fundus fluorescein angiography. We interpreted the visual acuity depending on the findings at the last visit of the patients.

The treatment for the anterior uveitis was topical corticosteroids and cycloplegics. In the case of posterior uveitis, we used systemic corticosteroids with or without immunosuppressive therapy. We administered fluorocortolone or prednisolone 0.5-1.5 mg/kg (80 mg maximum) per day for posterior uveitis, as first line of therapy. In the follow-up, we added immunosuppressants azathioprine (1-2.5 mg/kg per day) or cyclosporin A (5-15 mg/kg per day) as adjunct therapy, if needed. In case of failure of therapy, we combined both of the immunosuppressants with a moderate dose (0.5 mg/kg per day) of corticosteroids. If intolerance or failure occurred, then we tried substituting with interferon alpha 2a therapy (3-9 X 10^6 IU for 3 times per week). Colchicines are administered by Dermatology Department for mucocutaneous lesions. We did not use colchicines for ocular involvement. The appropriate systemic evaluation and laboratory investigations were performed to those who used immunosuppressant medication.

For the statistical analysis, we used the SPSS software package program (SPSS, Chicago, IL, U.S.A), version 16.0. For the differences between sexes, Mann-Whitney U test and Chi square test were used. The descriptive statistics were reported using median (min-max). We accepted (p) less than 5% as statistically significant.

RESULTS

Two hundred forty nine patients were included in the study. One hundred forty five patients (58.2%) were males and 104 patients (41.8%) were females. The median age at onset of the findings of BD was 29 (11-60) years; 29 (12-56) years in male and 29 (11-60) years in female patients, with no significant difference (p=0.861).

Table 1 summarizes the ocular and extraocular characteristics, and ocular complications. One hundred eighty (%72.3) patients had ocular involvement, and 147 (81.7%) of them were bilateral. One hundred twenty two (84.1%) of 145 male, and 58 (55.8%) of 104 female patients had ocular features. Male patients had ocular involvement rate that is statistically highly significant (p<0.001). The male-to-female ratio was 2.1:1. The most common ocular finding was vitritis, which was observed in 225 (68.8%) eyes. We observed anterior uveitis in 174 (53.2%) eyes with ocular involvement, and it was a solitary finding in 39 eyes (11.9%).

TABLE 1: Extraocular clinic manifestations of 259 Behçet's disease patients. Ocular findings and complications of 327 eyes of 180 ocular Behçet's disease patients.

Characteristics	Number (%) of patients (n=249)	Number (%) of eyes (n=327)
Extraocular findings		
Oral ulcers	249 (100%)	
Genital ulcers	189 (75.9%)	
Erythema nodosum	131 (52.6%)	
Papullopustular lesions	80 (32.1%)	
Pathergy test positivity	93 (37.4%)	
Ocular findings		
Vitritis		225 (68.8%)
Anterior uveitis		174 (53.2%)
Retinal vasculitis		72 (22%)
Papillitis		13(4%)
Ocular complications		
Epiretinal membrane		98 (30%)
Cataract		95 (29.1%)
Chronic cystoid macular edema		93 (28.4%)
Optic atrophy		49 (15%)
Retinal vein occlusion		29 (8.9%)
Optic disc or retinal neovascularization		7 (2.1%)
Phtisis bulbi		3 (0.9%)
Rubeosis iridis		2 (0.6%)

The visual acuity of the eyes with ocular BD at the last exam was 0.05 or worse in 86 (26.3%), and 0.5 or better in 209 eyes (63.9%). Twelve eyes (3.7%) had no light perception. One hundred and forty two eyes (43.4%) had a visual acuity of 1.0 or better. Median of visual acuity was 0.5 (0-1.0) for males and 0.61 (0-1.25) for females. Male patients had a statistically significant lower final visual acuity than female patients (p=0.008). The etiology for low visual acuity were; optic atrophy in 36 (41.9%), chronic cystoids macular edema in 32 (37.2%), central retinal vein occlusion in 8 (9.3%), phtisis bulbi in 3 (3.5%), vitritis in 3 (3.5%), retinal vein occlusion and optic atrophy in 2 (2.3%) and rubeosis iridis in 2 (2.3%) eyes.

In 22 patients (8.8%), we only used topical corticosteroids and cycloplegic treatment. Systemic corticosteroid therapy was used in 155 patients (86.1%). We used azathioprine in 66 (36.7%), cyclosporin A in 50 (27.8%), and interpheron alpha 2a in 15 patients (8.3%). Ninety seven patients (53.9%) were treated with systemic combination therapy. Dermatology department used colchicines for skin lesions and oral ulcers in 176 patients (97.8%).

DISCUSSION

Ocular involvement is a major potential cause of morbidity in BD. Relapsing uveitis attacks may cause progressive destruction of intraocular anatomy, and lead to serious functional vision loss. In the present study, we reviewed the ocular and extraocular findings of 249 patients with BD, residing in the Mediterranean Region of Turkey. Our clinic is a tertiary referral centre, and this may have caused a referral bias, which is a weakness of the study.

In general, the mean age at onset of BD is the third to fourth decade of life, but it can occur at any age from infancy to elderly.[1,8-11] The median age at onset of symptoms was 29 (11-60) years in our study. There was no significant difference regard-

ing age at onset between sexes. This finding is contrary to the statement that the male patients have a younger age of onset.[1]

We observed oral ulcers in all, and genital ulcers in 75.9% of the patients. These findings were similar to the literature.[3] We observed papullopustular lesions in 80 (32.1%) patients, which is lower compared to a ratio of 80% reported in other studies.[12] One hundred and thirty one (52.6%) patients presented with erythema nodosum and that is similar to the findings of Ghate and Jorizzo.[12] Pathergy test was positive in 93 patients (37.4%), which is lower compared to the older reports. Tugal-Tutkun et al. found similar lower frequencies of extraocular manifestations when compared to the general BD population.[9]

Eye involvement, along with central nervous system involvement, is the most serious manifestation of BD, and affects approximately 60-98% of patients.[1,5,13] We observed an ocular involvement rate of 72.3%. Similar to the literature, 81.6% of our cases had bilateral involvement.[9,14-17] The male to female ratio was 2.1:1 in the present study. Tugal-Tutkun et al. and Demiroglu et al. from Turkey reported the same ratio.[9,18] Kitaichi et al. from Japan found this ratio as 1.7:1. Krause et al. from Israel, and Kacmaz et al. from United States observed an even distribution between genders.[14,17,19] We believe that the differences between the ratios are due to the geographic variability in the clinical course.

The most frequent posterior segment finding of ocular BD is vitritis.[9,15,16,18] We observed vitritis, which was also the most common ocular finding in our series, in 225 eyes (68.8%). Retinal vasculitis, which is the most disastrous and fearful complication of ocular BD, was present in 72 (22%) eyes in our group. In a recent report by Krause et al., retinal vasculitis occurred in 16% of patients.[20] In the study by Kaçmaz et al., 21.8% of the patients suffered from vasculitis.[14]

Epiretinal membrane, occurring in 98 eyes (30%), was the most common complication in our study. Epiretinal membrane formation can be seen as a complication of any type of intraocular inflammation. In other studies, the percentage of epiretinal membrane ranges from 11.3 to 28.6%.[9,14,16,20] Another leading cause of vision loss in the present study was cataract formation found in 29.1% of the ocular BD eyes.

Despite the advancements in the medical therapy, loss of functional vision is still a severe complication of ocular BD. BenEzra and Cohen published a loss of useful visual acuity in 74% of ocular BD patients.[21] In their review, Boyd et al. stated that, ocular involvement in BD can be associated with blindness in 50-90% of cases.[22] However, the prevalence of legal blindness was reported in a range from 21 to 35% in recent studies.[17,20,23] We observed poor visual outcome in 86 eyes (26.3%). The differences in final visual acuity might be related to the regional differences in the clinical manifestations, and also to the fact that the clinical results of ocular BD have improved in the 1990s compared with the 1980s.[23,24] In our study, male patients had a statistically significant lower final visual acuity compared to female patients (p=0.008), which is consistent with the fact that BD runs a more severe course in males.[1,9,25]

The treatment of BD remains empirical and major discrepancies appear in approaches to treatment, despite the increased number of controlled trials.[26] In addition to topical corticosteroids for the treatment of anterior uveitis; systemic corticosteroids, azathioprine, cyclosporin A and colchicines are the drugs of choice in the treatment of severe posterior uveitis of ocular BD.[1,5,26-30] In recent studies, effective treatment with interferon alpha-2a has been demonstrated.[31,32]

CONCLUSION

Ocular BD still remains a blinding disease despite modern treatment methods. In the present study, 26.3% of the eyes lost functional vision due to the complications of uveitis. We have presented a retrospective epidemiological analysis of 249 BD patients from Southern Turkey. More than three- quarters of patients with BD had ocular involvement, and vitritis was the most common ocular finding. The male patients had a more frequent and serious ocular involvement, and there was no significant difference regarding the age at onset between sexes.

REFERENCES

1. Atmaca LS, Idil A, Batioĝlu F. A descriptive study on Behçet's disease. Acta Ophthalmol Scand 1996;74(4):403-6.
2. Yurdakul S, Yazici H. Behçet's syndrome. Best Pract Res Clin Rheumatol 2008;22(5): 793-809.
3. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med 1999;341(17): 1284-91.
4. Azizlerli G, Köse AA, Sarica R, Gül A, Tutkun IT, Kulaç M, et al. Prevalence of Behçet's disease in Istanbul, Turkey. Int J Dermatol 2003;42(10):803-6.
5. Deuter CM, Kötter I, Wallace GR, Murray PI, Stübiger N, Zierhut M. Behçet's disease: ocular effects and treatment. Prog Retin Eye Res 2008;27(1):111-36.
6. Nussenblatt RB. Uveitis in Behçet's disease. Int Rev Immunol 1997;14(1):67-79.
7. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990;335(8697):1078-80.
8. Koné-Paut I, Yurdakul S, Bahabri SA, Shafae N, Ozen S, Ozdogan H, et al. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. J Pediatr 1998;132(4):721-5.
9. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet disease: an analysis of 880 patients. Am J Ophthalmol 2004;138(3):373-80.
10. Tugal-Tutkun I, Urgancioglu M. Childhood-onset uveitis in Behçet disease:a descriptive study of 36 cases. Am J Ophthalmol 2003;136 (6):1114-9.
11. Yazici H, Yurdakul S, Hamuryudan V. Behçet's syndrome. Curr Opin Rheumatol 1999;11 (1):53-7.
12. Ghate JV, Jorizzo JL. Behçet's disease and complex aphthosis. J Am Acad Dermatol 1999;40(1):1-18; quiz 19-20.
13. Yates PA, Michelson JB. Behçet disease. Int Ophthalmol Clin 2006;46(2):209-33.
14. Kaçmaz RO, Kempen JH, Newcomb C, Gangaputra S, Daniel E, Levy-Clarke GA, et al.; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Group. Ocular inflammation in Behçet disease: incidence of ocular complications and of loss of visual acuity. Am J Ophthalmol 2008;146(6):828-36.
15. Atmaca LS. Fundus changes associated with Behçet's disease. Graefes Arch Clin Exp Ophthalmol 1989;227(4):340-4.
16. Ozdal PC, Ortaç S, Taşkintuna I, Firat E. Posterior segment involvement in ocular Behçet's disease. Eur J Ophthalmol 2002;12(5):424-31.
17. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behcet's disease: an international collaborative study. Br J Ophthalmol 2007;91(12):1579-82.
18. Demiroğlu H, Barişta I, Dündar S. Risk factor assessment and prognosis of eye involvement in Behcet's disease in Turkey. Ophthalmology 1997;104(4):701-5.
19. Krause I, Yankevich A, Fraser A, Rosner I, Mader R, Zisman D, et al. Prevalence and clinical aspects of Behcet's disease in the north of Israel. Clin Rheumatol 2007;26(4):555-60.
20. Krause L, Köhler AK, Altenburg A, Papoutsis N, Zouboulis CC, Pleyer U, et al. Ocular involvement in Adamantiades-Behçet's disease in Berlin, Germany. Graefes Arch Clin Exp Ophthalmol 2009;247(5):661-6.
21. Benezra D, Cohen E. Treatment and visual prognosis in Behçet's disease. Br J Ophthalmol 1986;70(8):589-92.
22. Boyd SR, Young S, Lightman S. Immunopathology of the noninfectious posterior and intermediate uveitides. Surv Ophthalmol 2001; 46(3):209-33.
23. Takeuchi M, Hokama H, Tsukahara R, Kezuka T, Goto H, Sakai J, et al. Risk and prognostic factors of poor visual outcome in Behcet's disease with ocular involvement. Graefes Arch Clin Exp Ophthalmol 2005;243(11):1147-52.
24. Yoshida A, Kawashima H, Motoyama Y, Shibui H, Kaburaki T, Shimizu K, et al. Comparison of patients with Behçet's disease in the 1980s and 1990s. Ophthalmology 2004;111 (4):810-5.
25. Yazici H, Tüzün Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdoğan H, et al. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis 1984;43(6):783-9.
26. Yazici H, Yurdakul S, Hamuryudan V. Behçet disease. Curr Opin Rheumatol 2001;13(1):18-22.
27. Yazici H, Pazarli H, Barnes CG, Tüzün Y, Ozyazgan Y, Silman A, et al. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990;322(5):281-5.
28. Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancey K. Effectiveness of cyclosporin therapy for Behçet's disease. Arthritis Rheum 1985;28(6):671-9.
29. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. Lancet 1989;1(8647):1093-6.
30. Kazokoglu H, Saatçi O, Cuhadaroglu H, Eldem B. Long-term effects of cyclophosphamide and colchicine treatment in Behçet's disease. Ann Ophthalmol 1991;23(4):148-51.
31. Kötter I, Günaydin I, Zierhut M, Stübiger N. The use of interferon alpha in Behçet disease: review of the literature. Semin Arthritis Rheum 2004;33(5):320-35.
32. Alpsoy E, Durusoy C, Yilmaz E, Ozgurel Y, Ermis O, Yazar S, et al. Interferon alfa-2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. Arch Dermatol 2002;138(4):467-71.