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ORIGINAL PAPER

Pattern of uveitis in Behçet's disease in a referral center in Tunisia, North Africa

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Abstract The purpose of this study was to analyze the pattern of uveitis in Behçet's disease in Tunisia, North Africa. We retrospectively reviewed the clinical records of 62 patients (111 eyes) diagnosed with Behçet's uveitis (BU) at the Department of Ophthalmology, Fattouma Bourguiba University Hospital, Monastir, Tunisia, between January 1995 and December 2006. Forty-seven of 62 patients (75.8%) were men and 15 (24.2%) were women. Mean age at onset was 29.3 years. The average follow-up was 75.6 months. The most common extraocular clinical manifestations were recurrent oral ulcer in all patients and pseudofolliculitis in 52 patients (83.9%). Uveitis was bilateral in 79%. Initial best-corrected visual acuity was ≥20/40 in 41 affected eyes (36.9%) and <20/200 in 49 affected eyes (44.2%). Panuveitis (68 eyes, 61.3%) and posterior uveitis (38 eyes, 34.2%) were the most common forms, followed by anterior uveitis (five eyes, 4.5%). Retinal vasculitis was found in 89 eyes (80.2%). Most common complications included posterior synechiae (32.4%), cataract (31.5%), and cystoid macular edema (19.8%). Systemic corticosteroids were administered in 58 patients (93.5%). Immunosuppressive drugs were used in 22 patients (35.5%). Fifty-six affected eyes (50.5%) had final visual acuity ≥20/40 and 34 affected eyes (30.6%) had final visual acuity <20/200. In Tunisia, BU affects predominantly young men. Bilateral panuveitis associated with retinal vasculitis was the most common ocular manifestation. More than 50% of patients maintained a visual acuity of 20/40 or better, and immunosuppressive therapy probably contributed to the improvement of visual prognosis of these patients.

Keywords Epidemiology · Behçet's uveitis · Tunisia · North Africa

Introduction

Behçet's disease is a chronic multisystem inflammatory disease of unknown etiology in which the principal lesional process is an obliterative and necrotizing vasculitis that affects both the arteries and the veins in all organ systems [1]. The incidence and severity of the disease are variable according to the geographic area and the population studied. Behçet's disease is predominant in the Mediterranean basin, along the Silk Road, and in Japan [1–4].

The frequency of ocular involvement in patients with Behçet's disease is around 70%, and a relapsing remitting uveitis is the most typical form of ocular involvement [1]. In addition, Behçet's disease was found to be a leading cause of uveitis in areas where the incidence of this disease is high [1–3]. Tunisia, a

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North African country, is located in one of these areas, and Behçet's uveitis (BU) was found to be the most common cause of uveitis in this country [5].

The pattern of BU has been well documented in some countries where the disease is endemic [3, 6–12], and studies have shown similarities and distinct differences in epidemiologic profiles, ocular involvement, complications, and visual prognosis. However, recent data on BU from the North African region are scarce [13, 14], and published studies in the English literature are lacking.

The aim of our study was to identify the pattern of BU in a referral center in Tunisia, North Africa.

Materials and methods

From January 1995 to December 2006, 560 consecutive patients with uveitis were assessed at the Department of Ophthalmology of Fattouma Bourguiba University Hospital, Monastir, Tunisia. Of these patients, 62 had Behçet's disease. Our hospital is a referral center for a large area and also a care center, seeing patients that attend casualty department directly. The average follow-up was 75.6 (range 12–124) months. All patients met the classification criteria of the International Study Group for Behçet's disease [15] and had a systemic history. Patients who had ocular involvement other than uveitis were excluded.

At the initial visit, patients were asked to fill out a detailed questionnaire, providing a detailed history including ocular complaints and systemic symptoms. Complete ophthalmic examination was performed in all cases, including best-corrected Snellen visual acuity, slit-lamp examination, applanation tonometry, and dilated fundus examination with three-mirror lens. Fluorescein angiography was performed at presentation and during follow-up in all patients.

The type of uveitis was classified anatomically according to the 2005 classification criteria of the Standardization of Uveitis Nomenclature (SUN) Working Group [16]. The definition of retinal vasculitis was based on the observation of inflammatory or gliotic sheathing of the vessels or on the fluorescein angiographic findings of staining, leakage, and/or occlusion of the retinal vasculature. Papillitis was defined as optic-disc swelling and/or optic-disc hyperfluorescence on fluorescein angiography. Patients who develop total optic atrophy, occluded vessels that look like white cords, and diffuse retinal atrophy with variable scarring and pigmentation were defined as having end-stage disease [11]. Reports from patients' primary ophthalmologists, dermatologists, and rheumatologists were evaluated, and patients were referred to the related specialists, when required, during the follow-up visits.

Demographic data, including age at presentation, gender, and extraocular clinical manifestations of Behçet's disease were noted from the medical files of each patient. Ophthalmologic data were also analyzed, including age at onset of uveitis, laterality, type of uveitis (namely, anterior, posterior, or panuveitis), ocular complications, visual acuity, anti-inflammatory and immunosuppressive therapy administered, surgical procedures performed, and the follow-up period. Disease duration was defined as the time interval between the onset of uveitis and time of presentation.

During the study period of 12 years, treatment protocols were changed. In 1995, we first treated patients with systemic corticosteroids monotherapy given orally (1 mg/kg) or by intravenous pulse therapy (1 g/day for 3 consecutive days) followed by oral administration, and we added immunosuppressive agents, either azathioprine (2.5 mg/kg per day) or cyclosporin (3–5 mg/kg per day), in case of an elevated response threshold to corticosteroids or intolerable side effects. However, in 2001 we tried to avoid corticosteroid monotherapy, and immunosuppressive drugs were administered in patients with posterior segment involvement early in the follow-up. If the disease was still not controlled, a third drug was introduced (azathioprine if the second drug was cyclosporin or vice versa). Associated periocular or intravitreal corticosteroid injections (triamcinolone acetonide) were administered in unilateral panuveitis or posterior uveitis attacks. All patients with anterior uveitis attacks were treated with topical corticosteroids.

Informed consent was obtained from each patient for the administration of immunosuppressive agent(s). Colchicine treatment was administered by the patients' dermatologists or rheumatologists. The systemic treatments used are known to cause potentially severe side effects, and the patients were regularly followed by the Department of Internal Medicine. The cumulative systemic treatments and

the mean duration of systemic therapy were analyzed. Visual acuity was determined at presentation, and visual outcome was calculated at the end of the study period. We defined potential visual acuity as the best visual acuity recorded during the first remission at the beginning of the follow-up. To analyze new loss of useful vision (≤20/200) irreversibly over the follow-up period, we estimated the cumulative survival of eyes with a potential visual acuity >20/200.

For data analysis, a computer-oriented patient database having the same format as the data form was constructed using the Microsoft Access 98 for Windows. Analysis of ocular findings and complications was based on the proportion of eyes that had these features at any visit. For differences between genders, the χ^2 test was used. Probability index (P) <5% was accepted as statistically significant.

Results

Mean age at presentation was 34 (range 16–57) years, and mean age at onset of uveitis was 29.3 (range 6–45) years. Forty-seven patients (75.8%) were men and 15 (24.2%) were women. Male-to-female ratio was 3.1:1. Extraocular clinical manifestations of Behçet's disease are shown in Table 1. All patients had recurrent oral ulcers. The second most common extraocular clinical manifestation was pseudofolliculitis (83.9%), followed by genital ulceration (80.7%). At presentation, the mean disease duration was 4.5 years. The total number of involved eyes was 111 (82 eyes in men and 29 eyes in women). The laterality of ocular involvement according to the follow-up period is shown in Table 2. Ocular involvement was bilateral in 49 (79%) and unilateral in 13 (21%) patients. One third of our patients with unilateral involvement had more than 5 years of follow-up. Thirty-five of 47 male (74.5%) and 14 female (93.3%) patients had bilateral involvement. The laterality of ocular involvement did not differ significantly among genders ($P = 0.15$). Mean age at onset of uveitis was 29.4 (range 11–44) years in men and 29.3 (range 6–45) years in women ($P = 0.18$). Eight patients (12.9%) had their first uveitis attack under the age of 20 years. No patient was identified to have onset of uveitis at 50 years or older.

Initial best-corrected visual acuity ranged from light perception to 20/20 (mean 20/45). It was ≥20/40 in 41 affected eyes (36.9%) and <20/200 in 49 affected eyes (44.2%). It was 20/200 or less in 27 of 82 eyes (32.9%) in men and ten of 29 eyes (34.5%) in women ($P = 0.5$). Mean initial visual acuity was ≥20/40 in 12 of 40 affected eyes (30%) of patients who presented before 2001 and in 31 of 71 affected eyes (43.7%) of patients who presented after 2001 ($P = 0.2$). It was <20/200 in 20 of 40 affected eyes (50%) in patients who presented before 2001 and in 17 of 71 affected eyes (23.9%) of patients who presented after 2001 ($P = 0.006$).

The classification of uveitis with respect to gender is shown in Table 3. The most frequent type of uveitis in both genders was panuveitis (61.3%). The ocular findings and comparison between genders are shown in Table 4. Hypopyon was noted in only six eyes (5.4%). Vitritis and retinal vasculitis were the most common findings of uveitis and were eventually observed in every patient with posterior uveitis or panuveitis (84.7% and 80.2%, respectively). Retinal vasculitis was more common in men ($P = 0.04$). The second most common ocular finding was papillitis (64 eyes; 57.7%). Retinitis was noted in 32 eyes (28.8%).

Disc hyperfluorescence was observed in all eyes with posterior segment involvement. Ischemic non-perfused areas were noted in 44 eyes (39.6%), and there were retinal new vessels in four eyes (3.6%). Complications observed and the comparison between

Table 1 Extraocular clinical manifestations of Behçet's disease

Findings	$N = 62$	Percent
Recurrent oral ulcers	62	100
Genital ulceration	50	80.7
Pseudofolliculitis	52	83.9
Pathergy's test +	39	62.9
Arthritis	31	50
Other findings	17	27.5

Table 2 Follow-up period and laterality of involvement at the end of follow-up

Type of involvement	<1 year		1–5 years		>5 years	
	N	%	N	%	N	%
Unilateral ($N = 13$; 21%)	2	15.4	7	53.8	4	30.8
Bilateral ($N = 49$; 79%)	20	40.7	17	35.1	12	24.2
Total ($N = 62$)	22	35.5	24	38.7	16	25.8

Table 3 Type of uveitis found by the end of follow-up and comparison of proportions between genders

Type of uveitis	Total eyes		Men		Women		*P* value
	N = 111	%	*N* = 82	%	*N* = 29	%	
Anterior uveitis	5	4.5	3	3.7	2	6.9	0.36
Posterior uveitis	38	34.2	30	36.6	8	27.6	0.51
Panuveitis	68	61.3	49	59.7	19	65.5	0.74

Table 4 Ocular findings observed at presentation or during follow-up and comparison of proportions between genders

	Total eyes		Men		Women		*P* value
	N = 111	%	*N* = 82	%	*N* = 29	%	
Hypopyon	6	5.4	3	3.6	3	10.3	0.34
Vitritis	94	84.7	73	89	21	72.4	0.06
Retinal vasculitis	89	80.2	70	85.4	19	65.5	0.04
Retinitis	32	28.8	25	30.5	7	24.1	0.68
Retinal hemorrhages	26	23.4	21	25.6	5	17.2	0.5
Papillitis	64	57.7	49	59.7	15	51.7	0.59

genders is summarized in Table 5. Overall, persistent posterior synechiae was the most common complication and was observed in 36 eyes (32.4%). Cataract constituted the second most common complication, occurring in 35 eyes (31.5%). Twenty-two eyes (19.8%) developed macular edema. Optic atrophy was observed in 15 eyes (13.5%). Branch retinal vein occlusion occurred in nine eyes (8.1%). Four eyes (3.6%) had end-stage disease.

Phthitis bulbi occurred in one eye (0.9%). There were no statistically significant differences in the proportion of complications between men and women. Four patients (6.4%) were treated with topical corticosteroids only. Systemic treatment is summarized in Table 6. Systemic corticosteroids were administered in 58 patients (93.5%). In 22 patients (35.5%), immunosuppression with a combination regimen was administered. The primary adjunction of an immunosuppressive to the steroids was performed in ten patients (16.2%); nine of these patients (90%) presented after 2001. In patients who presented before 2001, the adjunction of an

Table 5 Ocular complications observed at presentation or during follow-up and comparison of proportions between genders

	Total eyes		Men		Women		*P* value
	N = 111	%	*N* = 82	%	*N* = 29	%	
Posterior synechiae	36	32.4	24	29.3	12	41.4	0.33
Cataract	35	31.5	28	34.1	7	24.1	0.44
Macular edema	22	19.8	18	21.9	4	13.8	0.49
Epiretinal membrane	19	17.1	13	15.8	6	20.7	0.57
Optic atrophy	15	13.5	13	15.8	2	6.9	0.34
Intraocular pressure rise	9	8.1	6	7.3	3	10.3	0.69
Branch retinal vein occlusion	9	8.1	9	11	0	0	0.1
Disc/retinal neovascularization	6	5.4	4	4.9	2	6.9	0.56
Iris neovascularization	7	6.3	4	4.9	3	10.3	0.37
Intravitreal hemorrhage	4	3.6	2	2.4	2	6.9	0.27
End stage disease	4	3.6	4	4.9	0	0	0.57
Neovascular glaucoma	3	2.7	2	2.4	1	3.4	1
Retinal detachment	1	0.9	0	0	1	3.4	0.26
Phtysis bulbi	1	0.9	0	0	1	3.4	0.26

Table 6 Systemic treatment

Treatment	Group 1 (*N* of patients = 24)	Group 2 (*N* of patients = 38)	Percent
Systemic corticosteroids	22	37	95
Colchicine	15	13	45
Immunosuppressive	4	18	35.5
Azathioprine	1	14	24.2
Azathioprine + cyclosporin A	–	3	4.8
Azathioprine + cyclophosphamide	1	–	1.6
Cyclophosphamide	2	1	4.8

Group 1: patients who presented before 2001; Group 2: patients who presented after 2001

immunosuppressive to the steroids was motivated to lower the dosage in two patients because of intolerable corticosteroid-induced side effects and, in one patient, because of uncontrolled disease. Sixteen patients (25.8%) were treated with periocular corticosteroid injections in combination with systemic treatment and four patients (6.4%) with intravitreous corticosteroid injections in combination with systemic treatment.

Mean duration of systemic corticosteroid treatment was 15 months, and mean duration of immunosuppressive treatment was 26 months.

Fourteen eyes (12.6%) of ten patients underwent cataract surgery. Pars plana vitrectomy was performed in four eyes (3.6%). Indications for pars plana vitrectomy were vitreitis in two eyes, epiretinal membrane in one eye (0.9%), and macular edema in one eye (0.9%). Retinal laser photocoagulation was performed in four eyes (3.6%) for extensive capillary nonperfusion areas with disc/retinal neovascularization. Three eyes (2.7%) with neovascular glaucoma underwent transscleral cyclophotocoagulation. Fifty-six affected eyes (50.4%) had final visual acuity ≥20/40 and 34 (30.6%) had final visual acuity <20/200. Thirty-seven percent of affected eyes of patients who presented before 2001 had final visual acuity <20/200, with a mean follow-up of 68.9 months. Twenty-one percent of affected eyes of patients who presented after 2001 had final visual acuity <20/200, with a mean follow-up of 34 months ($P = 0.05$) (Table 7).

Potential visual acuity was analyzed in 81 eyes, because 30 eyes did not have follow-up. Potential visual acuity was <20/200 in 15 eyes (18.5%). Of the 54 eyes with a potential visual acuity >20/200, no patient lost useful vision irreversibly during follow-up.

Table 7 Final visual acuity (VA) in 111 affected eyes of 62 patients with Behçet's uveitis and comparison of proportions between two groups of patients presented before and after 2001

Final VA	Group 1		Group 2	
	N (eyes) = 40	%	*N* (eyes) = 71	%
≥20/40	21	52.5	41	57.7
20/200–20/40	4	10	15	21.1
<20/200	15	37.5	15	21.1

Group 1: patients who presented before 2001, Group 2: patients who presented after 2001

($P = 0.05$)

Discussion

BU is a chronic recurrent disease characterized by severe inflammation that may cause significant damage to the intraocular structures [1]. However, the clinical course and severity of the disease varies geographically, and several risk factors have been implicated to be associated with a severe course and a poor visual prognosis. Given continuing globalization, epidemiological studies on BU in different geographic areas or populations are important, as their results provide relevant clinical and research applications. For this study, we reviewed the medical records of 62 consecutive patients with BU from the North Africa region.

Our data showed a mean age at onset of uveitis (29.3 years), which was consistent with results of most previous reports (25–30 years) [9–12]. However, in a Japanese series with BU, the mean age at onset was around 35 years, similar to our patients [3, 17]. Findings from our study, consistent with those from a recent, large study [11], showed that men were more frequently involved than were women. The male-to-female ratio was 3.1:1 in our study. In two

studies from Turkey, that ratio was slightly lower (2.1:1) [8, 11], and in two other reports, the ratio was found to be approximately the same as ours [9, 12]. However, a higher ratio (4:1) was reported in a study from Switzerland; [10] in that study, there were different ethnic origins.

The frequency of extraocular findings has not been reported in most studies of patients with BU. In our study, the frequency of extraocular findings was found to be similar to that in the general Behçet's disease population [18, 19]. However, the frequency of extraocular findings was found to be lower in recent studies from Turkey [11] and Brazil [20]. Most previous studies have shown that bilateral involvement (78–95%) was more commonly encountered than was unilateral involvement [8–11, 20], which is consistent with results of our study. BenEzra et al. mentioned bilateral involvement in all of their patients [21]. Tugal-Tutkun et al. suggested that differences in the number of patients analyzed and in the follow-up period may have affected the laterality data reported in the literature [11]. The fact that one third of our patients with unilateral involvement had more than 5 years of follow-up suggested that BU may remain unilateral at least in some patients [11].

Posterior segment involvement in the form of posterior uveitis (30–53%) or panuveitis (44–60%) is the most common type of involvement in all series as well as in our study [8–10, 12, 20]. However, a lower rate of posterior uveitis (8%) was reported in a study from Switzerland [10]. The rate of anterior uveitis (4.5%) in our series was slightly lower than that in most previous studies (10–12%) [10, 11]. However, in a Japanese series, a lower proportion of patient with anterior uveitis was reported (2%) [17].

The most common findings observed at presentation or during follow-up in our patients with BU were retinal vasculitis and vitreitis. Similarly, results of most previous studies showed that both are consistent findings of posterior segment involvement [11, 12]. Papillitis was the third most common finding of BU (57.7%) in our series. Similarly, Yang et al. recently reported a high proportion of papillitis (67.3%) [12], whereas Tugual-Tutkun [11] and Ouazzani [14] reported a lower frequency (5.5% and 10%, respectively). Fluorescein angiography revealed leakage from the optic disc even in eyes without clinically detectable papillitis. Differences in the definition of papillitis may have resulted in variable frequencies reported [10, 11, 14]. The rate of retinitis (28.8%) in our population was lower than that reported in previous studies [9, 11, 12]. This could be explained by its transient nature and difficulty in visualizing the fundus when frequently vitreous haze accompanied the inflammatory episode.

Macular edema was the most common complication of BU, with variable frequency (29.7–63%) [1, 11, 12, 17, 22]. We found a lower frequency of macular edema (19.8%). Similarly, Ozdal et al. [9] reported macular edema in only 11.3% of all cases of BU. Other complications reported were cataract (17–38%), secondary glaucoma (6–19%), posterior synechiae (9–26%), branch retinal vein occlusion (5–10%), and optic atrophy (18–26%) [1, 9–11, 14, 17]. In our study, the rate of posterior synechiae (32.4%) was somewhat higher and that of optic atrophy (13.5%) was slightly lower. Previous studies reported that the progression of uveitis is worse in male Behçet's patients [11, 12, 17]. In our study, only retinal vasculitis was more common in men, and there were no significantly differences in the proportion of sight-threatening complications between men and women.

BenEzra et al. found that despite intensive follow-up and treatment, 74% of eyes lost useful visual acuity 6–10 years after the onset of uveitis [21]. In contrast, recent data, consistent with our results, showed a lower proportion of affected eyes with final visual acuity <20/200 [10–12, 23].

We found that patients who presented after 2001 had a better final visual acuity than patients who presented before 2001. This might be explained by the use of immunosuppressive drugs as first-line therapy after 2001. However, shorter follow-up and disease duration in this group might be a bias. Furthermore, initial visual acuity was better in patients treated after 2001 than in patients treated before 2001. This might be explained by a trend to milder disease after 2001.

Other previous studies showed that with immunosuppressive treatment approach, visual prognosis in Behçet's disease may further improve [1, 11, 18]. However, a recent international collaborative study emphasized that Behçet's disease is still a blinding disorder despite modern treatment, with one quarter of the patients becoming blind [24]. Patients with BU who are resistant to conventional immunosuppressive

therapy may benefit from new drugs, such as interferon-alpha or antitumor necrosis factor (anti-TNF), such as infliximab [25–27]. We think our patients could benefit from more aggressive therapy, but there are limitations regarding the cost of biologic agents in our country.

In summary, in a hospital population in Tunisia, BU starts frequently around the end of the third decade and had a male predominance. Bilateral panuveitis associated with retinal vasculitis was the most common ocular manifestation. Severe complications such as macular edema and optic atrophy were relatively rare. More than 50% of patients maintained a visual acuity of 20/40 or better, and immunosuppressive therapy probably contributed to the improvement of visual prognosis of these patients.

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