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Changing pattern of clinical manifestations of Behçet's disease in Tunisia: comparison between two decades

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Abstract

Objectives: To investigate the changes over time in extraocular and ocular manifestations of Behçet's disease (BD) in Tunisian patients.
Material and methods: Retrospective study of 246 patients divided into two groups: group 1 (147 patients examined from 1995 to 2005) and group 2 (99 patients examined from 2006 to 2017).
Results: Active or scarred genital ulcers observed by physician at presentation were significantly less frequent in group 2 (47.2% vs. 29.6%; $p = 0.007$), as were articular involvement (50.3% vs. 34.7%; $p = 0.016$) and erythema nodosum (18.4% vs. 8.1%; $p = 0.024$). One hundred-seven patients (43.5%) developed ocular manifestations during the 23-year study period. Intermediate uveitis was significantly more frequent in group 2 than in group 1 (11.7% vs. 28.4%; $p = 0.003$), and posterior uveitis less frequent in group 2 than in group 1 (34.2% vs. 19.7%; $p = 0.016$). Patients from group 2 were more likely to have macular edema (19.8% vs. 45.6%; $p = 0.001$). However, better visual prognosis, with a lower rate of legal blindness, was noted in group 2.
Conclusions: Changes over time included a decrease in the rate of articular involvement and cutaneous involvement. There was an increase in the rate of intermediate uveitis and a decrease in the rate of posterior uveitis over time. Despite an increase in the rate of macular edema, there was an improvement in visual prognosis, with less legal blindness over time.

Key words: Behçet's disease, uveitis, eye, epidemiology.

Introduction

Behçet's disease (BD) is an auto-inflammatory systemic disease, particularly prevalent in Mediterranean, Middle Eastern and Far Eastern countries. It is mainly characterized by recurrent oral and genital aphthosis associated with ocular manifestations. It may also involve, in a lesser extent, the gastro intestinal tract, joints and the central nervous system [1–4].

Behçet's disease can occur at any age but usually affects young adults between the second and the forth decade of life [2, 4, 5]. Typically a male predominance is reported [1, 2, 4, 6–9], although this has not been universally observed [6, 10, 11].

The disease runs a more severe course among males and youngsters [7–9]. Ocular involvement is common in BD, occurring in 18% to 70% [3, 6, 12, 13], with uveitis ranking first among ophthalmological manifestations.

On the other hand, BD is among major identifiable causes of non-infectious uveitis in endemic countries [13–15]. Panuveitis is the most common form of uveitis in BD [4], characterized by sudden onset, and recurrent exacerbations. This may lead to irreversible structural retinal changes and subsequent blindness, unless prompt diagnosis and management [5].

Recent data suggest that epidemiological and clinical expression of BD are changing over time [4, 16, 17]. A tendency toward milder forms of the disease was noticed in-

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cluding a shift in the patterns of organ involvement, with better visual prognosis and better overall clinical outcomes. This tendency has been reported in some countries [16, 17] but is yet to be confirmed in others. English publications on BD from North Africa are scarce [2], and data on the changes over time in the pattern of extraocular and ocular manifestations are lacking.

Our objective was to investigate the changes over time in extraocular and ocular manifestations of Behçet's disease in Tunisian patients.

Material and methods

We conducted a retrospective descriptive and comparative study including patients with BD seen from January 1995 to December 2017 at the Internal Medicine and Ophthalmology Departments in Fattouma Bourguiba University Hospital, Monastir, Tunisia. Patients were divided into two groups: group 1 included patients diagnosed with BD during the first decade between 1995 and 2005 and group 2 enrolled patients diagnosed with BD between January 2006 and December 2017.

All patients fulfilled the International Study Group for Behçet's Disease (ISGBD) criteria [18]. The demographic, clinical and biological characteristics of the patients were recorded. The onset of BD was defined as the time when BD-related symptoms first occurred. Neuro-Behçet disease (NBD) was defined according to the International Consensus Recommendation (ICR) criteria for NBD diagnosis [19].

Diagnosis of cardiovascular and gastrointestinal involvement was based on clinical examination and imaging techniques. Inflammatory arthralgia or arthritis, which was defined as the presence of any episode of either swelling, redness, or heating of the involved joints, not related to a specific cause, was considered to be a manifestation of BD.

Diagnosis of ocular involvement was made when ophthalmological evaluation showed uveitis that was compatible with BD [4, 5]. Uveitis was classified into isolated anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis according to the Standardization of Uveitis Nomenclature (SUN) working group classification [20].

Patent retinal vasculitis was attested by the presence of fluffy or gliotic sheathing of the vessels and/or the evidence of retinal vascular staining and leakage on the fluorescein angiographic (FA) associated or not with retinal vascular occlusions. Isolated mild peripheral capillary leakage on FA was considered among intermediate uveitis features. Associated optic neuritis was screened by afferent pupillary reflex defect, optic disc edema and important leakage on FA.

Blindness was defined as a central visual acuity of 20/200 or worse with the best correcting lens. For each patient, we collected history of the prescribed medications. Statistical analysis was performed using Windows IBM SPSS Statistics Version 21.0 (IBM Inc., Chicago, IL, USA). Descriptive statistics included the mean (standard deviation) or median (interquartile range) as appropriate for continuous variables, and frequency (percentage) for categorical variables.

Epidemiological as well as ocular and extraocular features were compared between group 1 and group 2. Categorical variables were analyzed using the chi-square test or the Fisher exact probability test, as appropriate. Continuous variables were analyzed using the Student *t*-test. A value of $p < 0.05$ was considered as statistically significant. This study adhered to the tenets of the Declaration of Helsinki. Mean follow-up was 12 years ±6 years (extremes: 2–23 years).

Results

The study included 246 patients: 185 males (75.2%) and 61 females (24.8%) with a sex-ratio of 1.5. The clinical characteristics of both groups are summarized in Table I. Mean age at diagnosis was 32.67 ±10.61 years and mean age at first symptoms onset was 30.52 ±10.87. The youngest patient was 12 years old, while the oldest was 77 years old. There was no difference in the age of patients between group 1 and group 2.

Of the group one, 111 were males (75.5%) and 36 females (24.5%) with a sex-ratio of 3.08. In group 2, there were 74 males (74.7%) and 25 females (25.3%) with a sex-ratio of 2.96. A family history of BD was found in 20 patients of group 1 (17.1%) and in 9 patients of group 2 (9.1%) ($p = 0.086$). Comparative study between group 1 and 2 revealed no significant difference in onset symptoms. Bipolar aphthosis was the most common onset symptom, seen among 102 patients (41.46%), of whom 61 (41.5%) were from group 1 and 41 (41.4%) were from group 2.

Oral ulcers were the onset symptom among 39 patients (26.53%) from group 1 and among 31 patients (31.37%) from group 2. Vascular involvement was noted in 54 patients (21.95%) as follow: venous involvement in 49 patients (19.9%), articular involvement in 12 patients (4.87%) and combined involvement in 7 patients (2.84%). Regarding neurological involvement, 13 patients developed parenchymal manifestations (5.28%) and 9 developed non-parenchymal involvement (3.65%). No statistical difference in vascular or neurological involvement was noted ($p = 0.25$, $p = 0.46$ respectively).

Active or scarred genital ulcers whether reported by the patients or observed by the physician and erythe-

Table I. Changes over time in demographic and clinical findings in patients with Behçet's disease

Parameters	Group one (1995–2005) (*n* = 147)	Group two (2006–2017) (*n* = 99)	*p*-value
Mean age at onset (years)	30.17 ±10.39	30.97 ±11.48	0.59
Mean age at diagnosis (years)	32.14 ±9.70	33.35 ±11.69	0.4
Gender (sex-ratio)	3.08	2.96	0.89
Oral ulcers	144 (98)	99 (100)	0.153
Active or scarred genital ulcers observed by physician at presentation	60 (47.2)	29 (29.6)	**0.007**
Pseudofolliculitis	122 (83)	78 (78.8)	0.4
Erythema nodosum	27 (18.4)	8 (8.1)	**0.024**
Acneiform nodules	9 (7.1)	2 (2)	0.082
Articular involvement	74 (50.3)	34 (34.7)	**0.016**
Neuro-Behçet	14 (11)	8 (8.2)	0.46
Gastrointestinal involvement	1 (0.8)	1 (1)	0.84
Epididymo-orchitis	8 (10.3)	2 (2.7)	0.12
Vascular involvement	34 (27)	20 (20.4)	0.25
Ocular involvement	62 (42.2)	45 (45.5)	0.61

The data are presented as no. of patients (%).

ma nodosum acneiform nodules were significantly less frequent in group 2 than in group 1 at presentation (p = 0.007; p = 0.024 respectively).

Pathergy test performed in 128 patients (87%) from group 1 and in 71 patients (71.7%) from group 2 was positive in 56 patients (77.35%) and 42 patients (59.15%) respectively (p = 0.13). Articular manifestations were significantly less frequent in group 2 than in group 1 as they were seen in 34 (34.7%) and 74 (50.3%) patients, respectively (p = 0.016). Arthralgia concerned 61 patients (48.4%) in group 1 and 32 patients (32.7%) in group 2 (p = 0.018), whereas arthritis was diagnosed in 7 patients (5.6%) in group 1 versus 9 patients (9.2%) in group 2 (p = 0.29). No other relevant clinical difference was noticed between the two groups. HLA-B51 phenotype was found in 10 patients in group 1 (21.3%) (out of 47 patients tested) and in 7 patients from group 2 (17.9%) (out of 37 patients tested). The difference was statistically significant (p= 0.029).

On the other hand, eye involvement was the onset symptom among 10 patients (8.1%) from group 1 and among 6 patients (6.1%) from group 2 (p = 0.31). Comparative study between both groups at the final follow-up examination showed that there was a significant increase in the rate of intermediate uveitis, which was observed in 13 patients (11.7%) of group 1 versus 23 patients (28.4%) of group 2 (p = 0.003) (Table II).

Patients from group 2 developed more macular edema than those from group 1 (19.8 vs. 45.6%; p = 0.001). Conversely, neovascular glaucoma was less common in group 2 than in group 1 (6.3% vs. 1.2%; p = 0.082) (Table III).

Table II. Changes over time in ocular manifestations of Behçet's disease

Parameters	Group one (1995–2005) (*n* = 111)	Group two (2006–2017) (*n* = 81)	*p*-value
Uveitis			
Anterior uveitis	5 (4.5)	6 (7.4)	0.4
Intermediate uveitis	13 (11.7)	23 (28.4)	**0.003**
Posterior uveitis	38 (34.2)	15 (19.7)	**0.016**
Panuveitis	60 (54.1)	37 (45.7)	0.25
Retinal vasculitis	89 (80.2)	62 (76.5)	0.54
Optic neuritis	3 (5.26)	0	0.1
Episcleritis	0	1 (1.2)	0.24

The data are presented as no. of eyes (%).

At final follow-up examination, patients of group 2 had better visual prognosis, with significantly less legal blindness rate (27% vs. 12.3%; p = 0.013) (Table IV).

Regarding treatment options, colchicine was prescribed to 207 patients (84%) with cutaneous manifestations associated or not to another organ involvement. One hundred seventy-eight patients (72.35%) were treated with oral corticosteroids. Thirty-three patients (13.4%) received intravenous pulses of methylprednisolone. Cyclophosphamide was given to 25 patients (10.1%) and seven patients were treated with cyclosporine A

Table III. Ocular complications observed at presentation or during follow-up and comparison of proportions between the two periods

Parameters	Group one (1995–2005) (*n* = 111)	Group two (2006–2017) (*n* = 81)	*p*-value
Macular edema	22 (19.8)	37 (45.6)	**0.001**
Macular hole	3 (2.7)	3 (3.7)	0.69
Epiretinal membrane	22 (19.8)	31 (38.27)	0.17
Cataract	35 (31.5)	27 (33.3)	0.79
Ocular hypertension	9 (12.3)	6 (7.4)	0.3
Disc/retinal neovascularization	6 (5.4)	4 (4.9)	0.88
Intravitreal hemorrhage	4 (3.6)	2 (2.4)	0.65
Neovascular glaucoma	7 (6.3)	1 (1.2)	0.082
Retinal detachment	1 (0.9)	1 (1.2)	0.82
Phthisis bulbi	1 (0.9)	1 (1.2)	0.82

The data are presented as no. of eyes (%).

Table IV. Final visual acuity (VA) in patients with Behçet's uveitis and comparison of proportions between two groups of patients presented before and after 2005

Final visual acuity	Group one (1995–2005) (*n* = 111)	Group two (2006–2017) (*n* = 81)	*p*-value
≥ 20/40	62 (55.9)	54 (66.7)	0.13
20/200–20/40	19 (17.1)	17 (21)	0.5
< 20/200	30 (27)	10 (12.3)	**0.013**

The data are presented as no. of eyes (%).

(2.84%). Azathioprine was prescribed to 85 patients (34.5%) and oral anticoagulation was used in 43 patients (17.47%). Acetylsalicylic acid (Aspirin) was given in 126 patients (51.2%). Comparative study between the 2 groups showed that colchicine and acetylsalicylic acid were both significantly less frequently used in group 2 than in group 1, whereas azathioprine was significantly more frequently used in the more recent group ($p = 0.026$).

Discussion

Given continuing globalization of the world, changes over time in the pattern of clinical manifestations of BD in different geographic areas or population are important, as their investigation may provide relevant clinical and research information. To our knowledge, this is the first study to explore the changes in clinical expression of BD in Tunisia, a North African country. Results of our study, consistent with previous data [21], show that the mean age of our patients with BD was around 30 years and remained unchanged over time.

The proportion of men was also stable over time which is consistent with most previous data on BD around the world which show the sex-ratio to remain unchanged [21]. Conversely, a few recent reports show an increase in the rate of females among BD patients over time [22, 23].

Regarding systemic involvement in our patients with BD over time, we observed an unchanged frequency of oral ulcers, which are hallmarks of BD but with significantly less frequent active or scarred genital ulcers observed by physicians at presentation in group 2 than in group 1. Patients with active genital ulcers might be treated in primary or secondary care centers explaining then such a tendency.

Additionally, we noted that erythema nodosum tends to be less frequent over time as were acneiform nodules. A part from that, less frequent articular involvement, and a slight decrease in the rate of vascular and neurological manifestations were noted and a significant decrease in the positivity of the HLA-B51 phenotype among the tested patients was also noted. A larger cohort, with more extended study, is needed to confirm

this genetic phenotype change in Behçet's disease. Our results also show that the frequency of ocular involvement tended to remain stable over time despite an increased awareness of the disease morbidity and a better screening of ocular inflammation in Tunisia.

Our results, consistent with previous data [1, 4, 23, 24], show that the vast majority of our patients with Behçet's uveitis had posterior segment inflammation with or without associated anterior uveitis. Isolated anterior uveitis was rare. Based on the SUN working group anatomic classification of uveitis, patients presenting with vitreous changes without clinically evident retinitis, retinal vasculitis, or optic nerve involvement are diagnosed as having intermediate uveitis. The presence of peripheral retinal capillary leakage or mild optic disc hyperfluorescence are considered as associated findings and not as features of posterior uveitis [25, 26].

The rate of intermediate uveitis in our series is higher than that previously reported, with a significant increased rate in the second group as compared to the first group [4, 23]. The lower rate of intermediate uveitis in previous studies could be explained by a discrepancy in the diagnostic criteria used to classify posterior segment involvement. Intermediate uveitis probably was not consistently differentiated from posterior uveitis, and all retinal vascular and optic disc changes, regardless of their severity, were considered as posterior uveitis findings [4, 16, 23].

Our results show also a significant increase of macular edema prevalence over time. Overall, macular edema is the most common complication among patient with BD uveitis [4]. However, the tendency of this complication to increase over time is difficult to confirm. In previous study, macular edema was not individualized from other macular complications including macular atrophy, macular hole and macular ischemia. Nevertheless, the increasing availability of Optical Coherence Tomography (OCT) machines, leading to an earlier detection of macular edema, may explain this finding.

Regarding visual prognosis, we found an improvement of visual outcome with less legal blindness over time. Similar shifting in visual prognosis was reported in previous studies [16, 17, 23]. This may be by dint of better monitoring of BD patients resulting in earlier detection and more appropriate management of uveitis. The early use of immunosuppressive agents as first-line therapy for ocular BD and, more recently biologics (anti-TNF-α and interferon) has reduced BD-related ocular damage and subsequent irreversible vision loss [17, 27, 28].

The overall tendency toward milder disease, similar to previous data, may have several explanations [23]. Previous studies have implied that the change has resulted from improved environmental conditions, and possibly, better patient adherence to treatment [17, 23]. Personal dental hygiene, particularly, has drastically changed. Excessive exposure to microbials might trigger autoimmunity to yet unknown antigens by molecular mimicry, thereby promoting BD [29]. Reduced bodily flora, streptococcal antigens in particular – which exist as bacterial flora in the oral cavity, through improved hygiene may hinder culprit microorganisms, preventing autoimmune phenomenon. A close association between periodontal status and disease severity has been discussed [29]. This issue has not been addressed in this study.

In terms of acknowledged limitations, this study was confined to a retrospective, tertiary care center-based analysis which might exclude patients with milder forms of BD followed-up in primary and/or secondary care centers. The study was also limited by the disparity of the follow-up period between the two groups of patients which was obviously longer for the patients from the first group. Other symptoms may occur in patients from the second group in the future.

Conclusions

Future endeavors should include longitudinal observation to study the timeline of clinical manifestations in BD with greater details to determine whether this demographic and clinical trend on BD reflects a real change in the epidemiology of BD or an awareness of the severity of ocular involvement leading to better screening and management.

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The authors declare no conflict of interest.

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