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Review Article

Prognostic Factors of Uveitis in Behçet's Disease: A Tunisian Study Over 28 Years

Mouna Snoussi[1], Marwen Boughriba[1], Abir Derbel [1*], Mayeda Ben Hmad[1], Faten Frikha[1], Salma Gargouri[2], Amira Trigui[1] and Sameh Marzouk[1]

[1]*Department of internal medicine, Hedi Chaker Hospital, Sfax, Tunisia.*
[2]*Department of Ophtalmology, Habib Bourguiba Hospital, Sfax, Tunisia.*

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Corresponding:
abirderbel@gmail.com

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Abstract

Behçet's disease (BD) is an inflammatory disorder of unknown etiology, characterized by recurrent oral ulcers, genital ulcers, skin lesions, and ocular involvement. Ocular involvement occurs in 25 to 80% of patients. We report the data of our monocentric, retrospective study which conducted in our departement between 1996 and 2024 including patients diagnosed as BD and had uveitis confirmed by ophthalmological examination. Among the 343 patients with BD, 114 had ocular involvement, and 88 patients met the inclusion criteria for analysis. The mean age at BD diagnosis was 36,6 ± 11,34 years, while the mean age at uveitis onset was 36,2 ± 11,5 years. 36,8% were in the third decade of life. They were 67 men and 21 women. Uveitis manifested acutely in 52 patients (59%). It was the initial symptom of BD in 73 patients (61,9%). The most common symptoms were decreased visual acuity (72%), eye redness (42%), and eye pain (36,1%). Extraocular manifestations included oral aphthous ulcers (100%), genital ulcers (85,4%), necrotizing pseudofolliculitis (72,9%), a positive pathergy test (30,4%), joint involvement (28,6%), venous thrombosis (22,2%), neurological involvement (14%), and arterial involvement (7,6%). A total of 150 eyes were affected by uveitis (107 in men, 43 in women), with bilateral involvement in 67 patients (76,1%). The anatomical distribution showed that panuveitis with retinal vasculitis was the most common presentation (63 eyes, 42%), followed by isolated panuveitis (56 eyes, 37,3%). Retinal vasculitis was observed in 47 eyes, while papillitis accompanied uveitis in 34 eyes (22,7%) and retrobulbar optic neuritis in 18 eyes (12%). Fluorescein angiography, performed in 32 patients (36,4%), confirmed papillitis in 18 cases and revealed retinal vasculitis in 21 of patients examined. Initial visual assessment revealed that 36 eyes had VA < 1/10, 43 eyes (29,4%) had VA between 1/10 and 5/10, and 67 eyes (46,2%) had VA > 5/10. After treatment, the final visual outcomes showed improvement, with 23 eyes (15.9%) having a VA < 1/10, 33 eyes (22.8%) having a VA between 1/10 and 5/10, and 89 eyes (61,4%) achieving a VA > 5/10. Treatment outcomes were considered favorable in 61,4% of cases, partially favorable in 22,8% of cases, and unfavorable in 15,9% of cases. 98,8% of patients received Colchicine, 6 patients received NSAIDs, Seventy-three patients (96,1%) received systemic corticosteroid treatment. High-dose corticosteroids were administered to 64 patients and 45 patients (59,2%) received pulse therapy with methylprednisolone (1 g/day for 3 days). Immunosuppressive therapy was added in 27 cases (35.5%), including cyclophosphamide (22 cases), azathioprine (11 cases), and cyclosporine (4 cases) after failure of azathioprine and cyclophosphamide, only 1 case received Thalidomid. Cataract was the most common complication, affecting 45,5%, followed by posterior synechiae in 15,9%, optic atrophy in 14.8%, maculopathy in 12,5% and glaucoma in 2.4%. Relapses were observed in 30 patients (34,1%), with an average of 2 relapses per patient. Univariate analysis identified this factors as associated with a poor visual prognosis including initial visual acuity < 1/10 (p = 0.000), presence of optic atrophy (p = 0.01) and occurrence of ocular relapses (p = 0.008). Multivariate analysis confirmed 3 independent prognostic factors for poor visual outcome which are: the initial visual acuity < 1/10 (OR: 5.21, 95% CI: 1.13-23.86, p = 0.034), the ocular relapses (OR: 8.39, 95% CI: 1.48-47.4, p = 0.016) and the optic atrophy (OR: 18.04, 95% CI: 0.90-358.93, p = 0.058). Univariate analysis revealed associations between complications and age, initial visual acuity < 1/10, and bilateral uveitis. Multivariate analysis identified the following independent risk factors for ocular complications: Bilateral uveitis (OR: 4.65, 95% CI: 1.34-16.06, p = 0.015), initial visual acuity as a continuous variable (OR: 0.75, 95% CI: 0.60-0.93, p = 0.012), treatment with methylprednisolone bolus (OR: 4.53, 95% CI: 1.21-16.94, p = 0.025). Univariate analysis showed associations between relapses and initial visual acuity < 1/10 (p = 0.04) and posterior uveitis location (p = 0.041). Multivariate analysis confirmed only initial visual acuity < 1/10 as an independent risk factor for relapses (OR: 4.12, 95% CI: 1.38-12.26, p = 0.011).

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1. Introduction

Behçet's disease (BD) is a chronic multisystem inflammatory disorder of unknown etiology, characterized by recurrent oral ulcers, genital ulcers, skin lesions, and ocular involvement. The disease shows remarkable geographical variation in terms of prevalence and clinical manifestations, including in the Mediterranean basin. Recent epidemiological studies indicate that BD affects approximately 420 individuals per 100,000 in Turkey, with significant variations between regions [1, 2].

Ocular involvement occurs in 25 to 80% of patients, depending on the population studied. The characteristic ocular manifestation is recurrent non-granulomatous uveitis, often associated with retinitis, which can lead to blindness if not properly managed. Contemporary studies using optical coherence tomography angiography (OCTA) have revealed significant microvascular alterations with reduced vascular density in the superficial and deep retinal capillary plexuses [3–5].

The prognosis for ocular BM has improved in recent decades thanks to advances in immunosuppressive therapy and the introduction of biological agents, including anti-TNF agents and interferon-alpha [6, 7].

Despite these therapeutic advances, the identification of prognostic factors remains crucial for optimal patient management and appropriate treatment selection. Recent studies have identified various risk factors for poor visual prognosis, including male gender, younger age at disease onset, posterior segment involvement, and longer disease duration. However, data from North African populations remain limited, particularly regarding long-term outcomes and contemporary management strategies [8, 9].

This study aims to characterize the epidemiological profiles, clinical characteristics, and prognostic factors of ocular BM in a Tunisian cohort, while contextualizing the results within the current international literature and therapeutic landscape.

2. Materials and Methods

2.1. Study population and Data collection

This monocentric, retrospective study was conducted in the internal medicine department of Hédi Chaker University Hospital, Sfax, Tunisia, between January 1996 and December 2024.

Patients were included if they met the criteria of the International Study Group for Behçet's Disease (BD) and had uveitis confirmed by ophthalmological examination. The diagnosis required the presence of recurrent oral aphthae ($\geq$ 3 times/year) and at least two of the following minor criteria : genital aphthae, ocular lesions, skin lesions, or a positive pathergy test.

Exclusion criteria included: (1) other types of ocular involvement in BD without uveitis, (2) insufficient medical records regarding ocular involvement, and (3) follow-up duration $<$1 year.

The ophthalmological examination included measurement of initial visual acuity (VA), slit lamp examination, and fundus examination. Fluorescein angiography was performed in some cases to confirm posterior segment involvement. Uveitis was classified anatomically according to the criteria of the Standardization of Uveitis Nomenclature (SUN) working group.

2.2. Variables to be assessed

- An assessment of the patient's initial visual acuity (VA) was performed before and after treatment. The visual prognosis was assessed according to the level of post-therapeutic visual impairment: categorized as favorable (VA $>$5/10), partially favorable (VA 1/10–5/10), or unfavorable (VA $<$1/10).
- Ocular complications : Including cataract, optic atrophy, maculopathy, and synechiae.
- Recurrences : Defined as new inflammatory episodes occurring during follow-up or without ongoing treatment.

2.3. Statistical analysis

The data were analyzed using SPSS (version 20). Quantitative variables were expressed as means, standard deviations, and medians, and qualitative variables as frequencies and percentages. The normality of the distributions was verified using the Shapiro–Wilks test. Comparisons were performed using the Student's t-test or the Mann-Whitney test for two independent samples, and ANOVA or the Kruskal-Wallis test for more than two groups. Qualitative variables were compared using Pearson's chi-square test or, if necessary, Fisher's exact test. Prognostic factors were studied using univariate and multivariate logistic regression analysis. A $p<0.05$ was considered statistically significant.

3. Results

3.1. Epidemiological characteristics

Among the 343 patients with BD, 114 (33.2%) had ocular involvement, and 88 patients met the inclusion criteria for analysis. The mean age at BD diagnosis was 36,6 ± 11,34 years (14–70), while the mean age at uveitis onset was 36,2 ± 11,5 years (14–51). The highest frequency was observed during the third decade of life (36,8%). The male-to-female ratio was 2,19, with 67 men (76.1%) and 21 women (23.9%).

3.2. Clinical presentation

Uveitis manifested acutely in 52 patients (59%), subacutely in 9 patients (10,22%), and chronically in 27 patients (30.68%). It was noted that uveitis was the initial symptom of BD in 73 patients (61,9%), preceding the diagnosis of BD in 51 cases (67,1%) and occurring concurrently with the diagnosis in 20 cases (38,5%).

The most common symptoms were decreased visual acuity (72%), eye redness (42%), and eye pain (36,1%). Extraocular manifestations included oral aphthous ulcers (100%, inclusion criterion), genital ulcers (85,4%), necrotizing pseudofolliculitis (72,9%), a positive pathergy test (30,4%), joint involvement (28,6%), venous thrombosis (22,2%), neurological involvement (14%), and arterial involvement (7,6%).

3.3. Anatomical distribution and ophthalmological findings

A total of 150 eyes were affected by uveitis (107 in men, 43 in women), with bilateral involvement in 67 patients (76,1%). The anatomical distribution showed that panuveitis with retinal vasculitis was the most common presentation (63 eyes, 42%), followed by isolated panuveitis (56 eyes, 37,3%), anterior uveitis (45 eyes, 30%), posterior uveitis (24 eyes, 16%), and intermediate uveitis (18 eyes, 12%).

Retinal vasculitis was observed in 47 eyes, while papillitis accompanied uveitis in 34 eyes (22,7%) and retrobulbar optic neuritis in 18 eyes (12%). Fluorescein angiography, performed in 32 patients (36,4%), confirmed papillitis in 18 cases and revealed retinal vasculitis in 21 of patients examined.

3.4. Visual outcomes and response to treatment

Initial visual assessment revealed that 36 eyes (24,6%) had VA $<$ 1/10, 43 eyes (29,4%) had VA between 1/10 and 5/10, and 67 eyes (46,2%) had VA $>$ 5/10. After treatment, the final visual outcomes showed improvement, with 23 eyes (15.9%) having a VA $<$ 1/10, 33 eyes (22.8%) having a VA between 1/10 and 5/10, and 89 eyes (61,4%) achieving a VA $>$5/10.

Treatment outcomes were considered favorable in 61,4% of cases, partially favorable in 22,8% of cases, and unfavorable in 15,9% of cases. The overall rate of visual improvement demonstrates the effectiveness of contemporary therapeutic approaches.

3.5. Therapeutic management

98,8% of patients received Colchicine, 6 patients received NSAIDs, Seventy-three patients (96,1%) received systemic corticosteroid treatment. High-dose corticosteroids were administered to 64 patients (84 ,2%), and 45 patients (59,2%) received pulse therapy with methylprednisolone (1 g/day for 3 days). Immunosuppressive therapy was added in 27 cases (35.5%), including cyclophosphamide (22 cases), azathioprine (11 cases), and cyclosporine (4 cases) after failure of azathioprine and cyclophosphamide, only 1 case received Thalidomid.

3.6. Complications and disease progression

Ocular complications developed in several patients during follow-up. Cataract was the most common complication, affecting 40 patients (45,5%), followed by posterior synechiae in 14 patients (15,9%), optic atrophy in 13 patients (14.8%), maculopathy in 11 patients (12,5%) and glaucoma in 2 patients (2.4%).

Relapses of the disease took place in 30 patients (34,1%), with an average of 2 relapses per patient (range: 1-4) . The relatively high relapse rate highlights the chronic and recurrent nature of BD-related uveitis.

3.7. Analysis of prognostic factors

Factors associated with poor visual outcome (BCVA $<$1/10)

Univariate analysis identified several factors associated with a poor visual prognosis, including initial visual acuity $<$ 1/10 (p = 0.000), the presence of optic atrophy (p = 0.01) and the occurrence of ocular relapses (p = 0.008).

Multivariate analysis confirmed three independent prognostic factors for poor visual outcome:

1. Initial visual acuity $<$ 1/10 (OR: 5.21, 95% CI: 1.13-23.86, p = 0.034)
2. Ocular relapses (OR: 8.39, 95% CI: 1.48-47.4, p = 0.016)
3. Optic atrophy (OR: 18.04, 95% CI: 0.90-358.93, p = 0.058)

Factors associated with ocular complications

Univariate analysis revealed associations between complications and age, initial visual acuity $<$ 1/10, and bilateral uveitis.

Multivariate analysis identified the following independent risk factors for ocular complications:

1. Bilateral uveitis (OR: 4.65, 95% CI: 1.34-16.06, p = 0.015)
2. Initial visual acuity as a continuous variable (OR: 0.75, 95% CI: 0.60-0.93, p = 0.012)
3. Treatment with methylprednisolone bolus (OR: 4.53, 95% CI: 1.21-16.94, p = 0.025)

Factors associated with disease relapses

Univariate analysis showed associations between relapses and initial visual acuity $<$ 1/10 (p = 0.04) and posterior uveitis location (p = 0.041).

Multivariate analysis confirmed only initial visual acuity $<$ 1/10 as an independent risk factor for relapses (OR: 4.12, 95% CI: 1.38-12.26, p = 0.011).

4. Discussion

This study represents one of the most comprehensive analyses of prognostic factors in Behçet's disease (BD)-related uveitis in North Africa. It provides valuable insights into regional characteristics of this sight-threatening condition over an extended 28-year period. Our findings highlight several important trends, both consistent with and divergent from contemporary international literature, offering new perspectives on disease evolution and therapeutic advances.

4.1. Epidemiological Trends and Regional Characteristics

The frequency of ocular involvement in our cohort (33.2%) remains remarkably consistent with our previous Tunisian studies that reported rates of 32.2% in a multicentric study and with North African regional data indicating a prevalence of 39%. This consistency suggests stable epidemiological trends in the Maghreb region. This constancy over nearly three decades indicates that ocular BD continues to represent a significant health burden in North Africa. However, our prevalence is lower than that of some international series reporting up to 70% ocular involvement, potentially reflecting differences in study methodology, referral patterns, or genetic factors [10, 11].

The marked male predominance (76.1%) and mean age at uveitis onset (36 years) correspond to established BD trends, with a male-to-female ratio of 2.19 similar to that of many reported series. Recent studies from the AIDA Network BD registry in juvenile patients have shown similar male predominance in posterior segment involvement, suggesting this pattern may be consistent across all age groups [12, 13].

Regarding the incidence peak corresponding to the third decade (36.8%) in our study, this aligns with contemporary international data suggesting important clinical implications, as younger age of onset has been consistently associated with more severe disease progression and worse visual prognosis in several cohorts [12, 14, 15].

The spectacular increase in bilateral involvement compared to older Tunisian studies, from 49.4% to 76.1%, represents one of the most striking changes in our cohort. This increase likely reflects several factors: longer follow-up periods allowing bilateral progression, better diagnostic sensitivity, and potentially more aggressive phenotypes referred to our care center. The international literature consistently reports bilateral involvement in 63-100% of bipolar uveitis cases, with higher rates correlated with disease severity and duration [12, 13].

4.2. Clinical Presentation and Anatomical Distribution

The predominance of panuveitis with retinal vasculitis (42% of affected eyes) characterizes BD uveitis in our population, consistent with the vasculitic nature of this condition. This finding aligns with recent OCTA studies demonstrating significant microvascular alterations in BD patients, with reduced vascular density in both superficial and deep capillary plexuses, even during remission [1, 16, 17].

The high frequency of uveitis as the initial manifestation (61.9%) exceeds generally reported rates in the literature (10-20%) and recent pediatric series from the AIDA registry. This high frequency has crucial implications for ophthalmologic screening protocols that should be prioritized in patients with suggestive symptoms, even in the absence of complete BD criteria, also considering recent data showing that early and aggressive treatment significantly improves long-term outcomes [3, 18].

The high frequency of anterior uveitis in our series (30%), although unusual compared to many international studies reporting less than 10%, could reflect the inclusion of mixed anterior-posterior presentations or regional phenotypic variations. This finding emphasizes the importance of comprehensive anatomical evaluation, as recent studies have shown that even apparently isolated anterior uveitis in BD often presents subclinical posterior involvement detectable by advanced imaging [16].

4.3. Therapeutic Evolution and Visual Outcomes

The introduction of colchicine as first-line treatment in 98.8% of patients represents an interesting therapeutic approach, reflecting current knowledge of its anti-inflammatory and anti-angiogenic properties. Recent studies have confirmed colchicine's efficacy in reducing systemic and ocular manifestations of BD, with particular benefit in preventing thrombotic complications [19].

The visual improvement rate of 61.4% in our cohort occurs in the context of initially more severe disease (increased bilateral involvement, higher complication rates), suggesting therapeutic efficacy but remaining limited. Recent studies using contemporary biologic therapies report superior results, with meta-analyses showing significant improvements in visual acuity preservation and reduced relapse rates.

However, the high cataract formation rate of 45.5% underscores the crucial importance of early introduction of steroid-sparing agents and biologics, as demonstrated by recent controlled trials showing superiority of anti-TNF over conventional immunosuppressants [6, 19, 20].

While our cohort primarily reflects the pre-biological era, recent literature provides compelling evidence of the transformative impact of targeted therapies. Anti-TNF agents, particularly infliximab and adalimumab, have demonstrated superior efficacy in controlling inflammation, preventing relapses, and preserving visual acuity. A recent meta-analysis showed significant reduction in visual acuity logMAR values (MD = -1.5, 95% CI: -2.1, -0.01) with anti-TNF treatment, as well as substantial reduction in prednisolone requirements [6, 20].

Interferon alpha has emerged as another highly effective therapeutic option, with randomized controlled trials demonstrating superior efficacy compared to cyclosporine. The time to complete remission was significantly shorter with interferon alpha (3.3 vs 7.0 months), with better visual acuity preservation and sustained remission. This medication achieves response rates of 80-90% in refractory cases, with the additional advantage of not increasing tuberculosis risk [21, 22].

4.4. Prognostic Factors and Risk Stratification

Our confirmation of initial visual acuity below 1/10, ocular relapses, and optic atrophy as independent prognostic factors provides solid evidence for risk stratification. These results align with recent international studies, notably Iranian and Italian cohorts, confirming the universal applicability of these factors and adding similar prognostic factors, including panuveitis, posterior uveitis, retinal vasculitis, and longer disease duration to different populations. These findings support the development of risk stratification models for early identification of patients requiring aggressive treatment [12].

The association between bilateral involvement and increased complication risk (OR: 4.65) is a consistent finding across many studies and reflects the systemic inflammatory nature of BD. Recent studies using advanced imaging have refined our understanding of BD, with OCTA revealing subclinical involvement in apparently unaffected fellow eyes [12, 16, 17].

The identification of methylprednisolone pulse treatment as a risk factor for complications (OR: 4.53) likely reflects its use in severe cases rather than direct causality. However, this finding reinforces the importance of rapid introduction of steroid-sparing agents to minimize corticosteroid exposure and associated complications [3, 18].

4.5. Complication Profile

The complication profile in our series, where cataract predominates at 45.5%, reflects both longer follow-up and intensive corticosteroid use. This finding contrasts with recent studies reporting maculopathy as the most frequent complication and those referring to biologic treatments that reported improved complication profiles. The persistence of cataract as the main complication over 28 years underscores the need for early biologic intervention and optimization of corticosteroid-sparing strategies [19, 20].

Compared to older Tunisian studies, the relatively stable rates of optic atrophy (14.8%) and maculopathy (12.5%) suggest that despite overall visual improvement, severe structural complications persist. Recent studies using advanced imaging have shown that early detection of subclinical macular changes can predict future complications, enabling preventive therapeutic intensification [16].

4.6. Future Perspectives

Current therapeutic algorithms favor early aggressive treatment in cases of posterior segment involvement and unfavorable prognostic factors. EULAR recommendations support the use of anti-TNF agents or interferon alpha as first-line treatment for sight-threatening uveitis, with azathioprine and cyclosporine remaining important conventional options.

Recent advances in understanding BD pathophysiology have identified new therapeutic targets. Interleukin-1 inhibitors show promise in refractory cases, while JAK inhibitors represent an emerging therapeutic option. The integration of multimodal imaging, particularly OCTA and enhanced optical coherence tomography, especially those using artificial intelligence, improves both diagnosis and treatment response monitoring [3].

Precision medicine approaches integrating genetic profiling, biomarker analysis, and imaging phenotyping hold promise for individualized therapeutic strategies. The identification of patients likely to benefit from specific biologic treatments, based on their genetic background or inflammatory profile, could revolutionize therapeutic algorithms and improve outcomes while reducing costs.

4.7. Clinical Implications

Our findings have several immediate clinical implications. The high rate of inaugural uveitis justifies enhanced ophthalmologic screening in patients with suggestive symptoms of BD. The strong prognostic value of bilateral involvement and initial visual acuity justifies early and aggressive treatment in high-risk patients, potentially including first-line biologics in severe cases [18].

The considerable burden of complications, particularly cataract, underscores the need for integrated care models involving ophthalmology, rheumatology, and internal medicine.

Healthcare systems must prepare for the growing demand for biologic therapies while considering cost considerations and access limitations in developing countries.

The retrospective design and single-center nature of our study may limit its generalizability, particularly regarding treatment outcomes in the era of biologic therapies. Missing data and referral bias toward more severe cases may influence results.

However, the extended follow-up period and large cohort size provide valuable information on BD uveitis in North Africa, robust epidemiological data, and solid identification of prognostic factors. The consistency of our findings with international literature confirms their validity and relevance for clinical practice and underscores the importance of early screening, rapid aggressive treatment for high-risk patients, and the need for contemporary therapeutic approaches to optimize outcomes.

5. Conclusion

This comprehensive 28-year analysis of uveitis in North Africa reveals both concerning trends and therapeutic progress. While the burden of severe bilateral disease and its complications has increased, visual outcomes have improved despite more complex initial characteristics. The identification of robust prognostic factors enables risk stratification and personalized therapeutic approaches.

The study underscores the crucial importance of early and aggressive treatment, particularly in patients with poor prognosis. While our cohort primarily reflects conventional therapeutic approaches, contemporary biologic therapies offer better disease control and vision preservation. The integration of advanced imaging, genetic testing, and artificial intelligence promises further improvements in diagnosis, monitoring, and therapeutic choice.

Article Information

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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