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CLINICAL STUDY

Pattern of uveitis in a referral centre in Tunisia, North Africa

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Abstract

Aim **To analyse the pattern of uveitis in a referral centre in Tunisia, North Africa.**
Methods **The study included 472 patients with uveitis examined at the Department of Ophthalmology of Monastir (Tunisia) from January 1992 to August 2003. All patients had a comprehensive ocular and systemic history, including an extensive review of medical systems. 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. Standard diagnostic criteria were employed for all syndromes or entities of uveitis.**
Results **The mean age at onset of uveitis was 34 years. The male-to-female ratio was 1 : 1.1. Uveitis was unilateral in 282 patients (59.7%) and bilateral in 190 patients (40.3%). Anterior uveitis was most common (166 patients; 35.2%), followed by posterior uveitis (133 patients; 28.2%), panuveitis (100 patients; 21.2%), and intermediate uveitis (73 patients; 15.5%). A specific diagnosis was found in 306 patients (64.8%). The most common cause of anterior uveitis was herpetic uveitis (56 patients; 33.7%). Toxoplasmosis was the most frequent cause of posterior uveitis (51 patients; 38.3%). Intermediate uveitis was most commonly idiopathic (63 patients; 86.3%). Behçet's disease was the most common cause of panuveitis (36 patients; 36%), followed by Vogt–Koyanagi—Harada (VKH) disease (15 patients; 15%). A total of 16 patients (3.4%) suffered from blindness, and 59 (12.5%) from uniocular blindness.**
Conclusions **In a hospital population in Tunisia, the most common causes of uveitis were Behçet's disease, herpes simplex infection, toxoplasmosis, and VKH disease.**

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Introduction

Uveitis refers to intraocular inflammation involving not only the uveal tract but also the adjacent structures, including the retina and vitreous. It affects people from all parts of the world, and it is a significant cause of severe visual impairment, accounting for 10% of blindness in the Western world.[1] The pattern of uveitis is largely influenced by a multitude of factors, including genetic, ethnic, geographic, and environmental factors, diagnostic criteria, and referral patterns.[2] It also changes over time with the emergence or identification of newer uveitic entities and improvement of diagnostic techniques.

Given the continuing globalization of the world, epidemiological studies on uveitis in different geographic areas or populations are important, as their results provide relevant clinical and research applications. Numerous studies on pattern of uveitis in various geographic regions from Western countries and Asia have been published, showing similarities and distinct differences in epidemiologic profiles and aetiologies of uveitis.[3–22] Data on uveitis from Africa are scarce,[23,24] and there is a lack of studies from the North African region.

The objective of our study was to identify the pattern of uveitis in a major university hospital eye centre in Tunisia, a North African, south Mediterranean country with 350 ophthalmologists for its 10 millions inhabitants in 2003.

Materials and methods

The study included 472 consecutive patients with uveitis who were seen between January 1992 and August 2003 at the Ophthalmologic Department of Fattouma Bourguiba University Hospital, Monastir, Tunisia. Our hospital is a referral centre for a large area, and also a care centre seeing patients that attend directly the Casualty Department.

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All patients had a comprehensive ocular and systemic history, including an extensive review of medical systems. 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. Patients were classified according to the International Uveitis Study Group system[25] as having anterior uveitis, posterior uveitis, intermediate uveitis, or panuveitis. Acute uveitis was defined as sudden onset of intraocular inflammation lasting less than 3 months. Chronic uveitis was defined as intraocular inflammation lasting longer than 3 months. Patients were also classified with (1) nongranulomatous uveitis if they exhibited small endothelial keratic precipitates and the absence of iris nodules and/or choroidal granulomas, or (2) granulomatous uveitis if large 'mutton-fat' keratic precipitates, iris nodules and/or optic disc, and choroidal granulomas were seen. The unilateral or bilateral character of uveitis was also recorded.

Fluorescein angiography was undertaken in all patients with definite or questionable posterior segment involvement. Visual field testing, electrophysiology tests, and ocular ultrasonography were performed when indicated.

Depending on their anatomic classification, all patients underwent a standard protocol for uveitis, including complete blood cell count, erythrocyte sedimentation rate, HLA-B27 typing, serum fluorescent treponemal antibody absorption detection, serum angiotensin-converting enzyme, serum lysozyme, tuberculin skin testing, and chest radiography. Patients with diagnostic leads provided by the history, review of systems, or examination underwent specific directed tests. These tests included serologic testing for toxoplasmosis, Lyme disease, *Bartonnella henslae*, *Rickettsia conorii*, toxocara, antinuclear antibodies, HLA-A29, imaging studies, and aqueous humour analysis for intraocular synthesis of antitoxoplasmic antibodies.

The diagnosis of Behçet's disease was made in patients fulfilling the diagnostic criteria of the International Study Group for Behçet's disease.[26]

The diagnosis of herpetic anterior uveitis was based on suggestive clinical features: positive history for HSV keratitis, clinical observation of corneal sensation depression, stromal keratitis, high intraocular pressure, and iris atrophy.

The diagnosis of ocular toxoplasmosis was based on the finding of focal retinitis associated with typical retinochoroidal scar in a patient with positive toxoplasma serology. In doubtful cases, the intraocular production of antitoxoplasmal antibodies was assessed by aqueous humour analysis (Goldmann–Witmer coefficient greater than 3).

The diagnosis of Vogt–Koyanagi–Harada (VKH) disease was made according to the diagnostic criteria established by the American Uveitis Society in 1978.[27] The revised diagnostic criteria for VKH disease were used for patients observed after June 2001.[28]

The diagnosis of confirmed sarcoidosis was made in cases of positive histological examination of biopsy specimen and of presumed sarcoidosis in the presence of at least two of the following three diagnostic criteria: increased serum levels of angiotensin-converting enzyme and/or lysozyme, cutaneous anergy, and positive chest radiography and/or CT scan.

All other systemic diseases and specific clinical ocular entities were diagnosed according to current diagnostic criteria.

The term idiopathic uveitis was used whenever the intraocular inflammation could not be attributed to an underlying systemic disease or specific ocular entity.

After the diagnostic procedures were completed, the patients were classified as having infectious uveitis, uveitis associated with noninfectious systemic diseases, specific ocular entities, or idiopathic uveitis.

Blindness was defined as visual acuity less than 20/400 in the better eye, and uniocular blindness as visual acuity less than 20/400 in one eye but better than 20/40 in the other eye.[29]

Results

The clinical and demographic characteristics of the 472 patients are shown in Table 1.

Recruitment of patients was as follows: 354 patients (75%) referred by ophthalmologists, 24 patients (5%) referred by general practitioners, and 94 patients (20%) attending directly our department. Ophthalmologists generally referred to us chronic or recurrent cases of uveitis, while general practitioners referred all patients suspected to have uveitis.

The mean age at onset of uveitis was 34 years (range 4–80 years). In all, 219 patients (46.4%) were between the ages of 20 and 40 years. In total, 47 (10%) of our patients were younger than 16 years and 36 (7.6%) were aged more than 60 years. No significant gender predominance was found (male–female ratio, 1 : 1.1). Follow-up ranged from 12 months to 11 years (mean follow-up 42 months). Uveitis was unilateral in 282 patients (59.7%) and bilateral in 190 patients (40.3%). There was a significant predominance of bilateral disease among patients with panuveitis (ratio, 3 : 2). Uveitis was chronic in 317 patients (67.2%), a predominance that was marked in patients with panuveitis (98.5%) and intermediate uveitis (100%). Nongranulomatous uveitis (89%) occurred more frequently than granulomatous uveitis (11%). Anterior uveitis was the most frequently occurring form

Table 1 General characteristics of the patients and distribution according to different classification criteria

	No. (%)
Referral pattern	
Ophthalmologists	354 (75)
General practitioners	24 (5)
Patients attending directly our department	94 (20)
Mean age	34.3 years (range 4–80 years)
Sex	
M	224 (47.5)
F	248 (52.5)
Mean follow-up	42 months (range 12–132 months)
Ocular involvement	
Unilateral	282 (59.7)
Bilateral	190 (40.3)
Chronologic	
Acute	155 (32.8)
Chronic	317 (67.2)
Type of inflammation	
Granulomatous	52 (11)
Nongranulomatous	420 (89)
Infectious vs noninfectious	
Infectious	137 (29)
Noninfectious	335 (71)

Table 2 Aetiologies of uveitis (total 472)

	No. of patients	*%*
Infectious disease		
Herpetic uveitis	56	11.9
Toxoplasmosis	51	10.1
Toxocariasis	7	1.5
Rickettsiosis	5	1.1
Tuberculosis	5	1.1
Acute retinal necrosis	4	0.8
Cytomegalovirus retinitis	3	0.6
Syphilis	3	0.6
Cat scratch disease	1	0.2
Fungal retinitis	1	0.2
Herpes zoster panuveitis	1	0.2
Total	137	29
Systemic disease		
Behçet's disease	58	12.3
Ankylosing spondylitis	8	1.7
Sarcoidosis (confirmed/presumed)	8 (3/5)	1.7
Nonspecific arthropathy (HLA-B27-positive)	5	1.1
Crohn's disease	4	0.8
Psoriatic arthritis	4	0.8
Juvenile idiopathic arthritis	3	0.6
Multiple sclerosis	3	0.6
Reiter's syndrome	1	0.2
Rheumatoid arthritis	1	0.2
Systemic lupus erythematosus	1	0.2
Tubulointerstitial nephritis	1	0.2
Ulcerative colitis	1	0.2
Total	98	20.1
Specific ocular condition		
VKH disease	21	4.4
Fuchs' heterochromic iridocyclitis	14	3
Multifocal choroiditis and panuveitis	8	1.7
Serpiginous choroiditis	7	1.5
APMPPE	5	1.1
Sympathetic ophthalmia	5	1.1
Posner–Schlossman syndrome	4	0.8
Acute idiopathic maculopathy	2	0.4
MEWDS	2	0.4
Punctate inner choroidopathy	2	0.4
Birdshot retinochoroidopathy	1	0.2
Total	71	15
Idiopathic	166	35.2

accounting for 35.2% of all patients, followed by posterior uveitis (28.2%), panuveitis (21.2%), and intermediate uveitis (15.5%).

For 306 of 472 (64.8%) patients with uveitis, a specific aetiologic diagnosis was established. In total, 166 patients (35.2%) were found to have idiopathic uveitis. Noninfectious uveitis occurred more frequently (71%) than infectious uveitis (29%). Among patients with noninfectious uveitis, 98 (20.1%) had an overlying systemic disease, and 71 (15%) had a specific ocular condition. The most common identified causes of uveitis in our series were Behçet's disease (12.3%), herpetic uveitis (11.9%), toxoplasmosis (10.1%), and VKH disease (4.4%; Table 2).

In the anterior uveitis group ($n=166$), a specific aetiologic diagnosis was made for 107 patients (64.5%). The most common diagnoses included herpetic infection (33.7%), HLA-B27-positive acute anterior uveitis with or without associated systemic disease (12.7%), and Fuchs' heterochromic iridocyclitis (8.4%; Table 3).

In the posterior uveitis group ($n=133$), a specific diagnosis was made for 119 patients (89.5%). The most frequent diagnoses were toxoplasmosis (38.3%), Behçet's disease (12.8%), serpiginous choroiditis (5.3%), and toxocariasis (5.3%; Table 4).

Among patients with panuveitis ($n=100$), 70 (70%) had a specific aetiologic diagnosis. Common diagnoses included Behçet's disease (36%) and VKH disease (15%; Table 5).

Intermediate uveitis ($n=73$) was most commonly idiopathic (86.3%). Sarcoidosis (8.2%) and multiple

Table 3 Causes of anterior uveitis

Causes	*No. of patients*	*%*
Herpetic uveitis	56	33.7
Fuchs' heterochromic iridocyclitis	14	8.4
Ankylosing spondylitis[a]	8	4.8
Behçet's disease	5	3
Nonspecific arthropathy (HLA-B27 +)	5	3
Psoriatic arthropathy[a]	4	2.4
Posner–Schlossman syndrome	4	2.4
Crohn's disease[a]	3	1.8
Juvenile idiopathic arthritis	3	1.8
Sarcoidosis	2	1.2
Reiter's syndrome[a]	1	0.6
Tubulointerstitial nephritis	1	0.6
Ulcerative colitis	1	0.6
Idiopathic	59	35.5
Total	166	100

[a]All these cases were HLA-B27+ (total number of HLA-B27+ uveitis = 21 (12.7%)).

Table 4 Causes of posterior uveitis

Causes	*No. of patients*	*%*
Toxoplasmosis	51	38.3
Behçet's disease	17	12.8
Serpiginous choroiditis	7	5.3
Toxocariasis	7	5.3
VKH disease	6	4.5
APMPPE	5	3.8
Rickettsiosis	5	3.8
Acute retinal necrosis syndrome	4	3
Syphilis	3	2.3
Cytomegalovirus retinitis	3	2.3
Acute idiopathic maculopathy	2	1.5
MEWDS	2	1.5
Punctate inner choroidopathy	2	1.5
Others[a]	5	3.8
Idiopathic	14	10.5
Total	133	100

APMPPE = acute posterior multifocal placoid pigment epitheliopathy; MEWDS = multiple evanescent white-dot syndrome.
[a]Birdshot retinochoroidopathy one case, cat scratch disease one case, Crohn's disease one case, fungal retinitis one case, and tuberculosis one case.

sclerosis (4.1%) were the most common systemic diseases associated with this type of uveitis (Table 6).

The most common complications encountered in our patients were cystoid macular oedema (23.3%), intraocular pressure elevation (>21 mmHg) (15.9%), and cataract (15.6%). A total of 16 patients (3.4%) suffered from blindness, and 59 (12.5%) from uniocular blindness.

Discussion

To the best of our knowledge, this study is the first to provide data on uveitis from the North African region.

Table 5 Causes of panuveitis

Cause	*No. of patients*	*%*
Behçet's disease	36	36
VKH disease	15	15
Multifocal choroiditis and panuveitis	8	8
Sympathetic ophthalmia	5	5
Tuberculosis	3	3
Others[a]	3	3
Idiopathic	30	30
Total	100	100

[a]Herpes zoster panuveitis one case, rheumatoid arthritis one case, systemic lupus erythematosus one case.

Table 6 Associated diseases in intermediate uveitis

Associated disease	*No. of patients*	*%*
Sarcoidosis	6	8.2
Multiple sclerosis	3	4.1
Tuberculosis	1	1.4
Idiopathic	63	86.3
Total	73	100

Findings from our study, consistent with those from previous reports, showed that males and females were almost equally affected, and that age at onset of uveitis widely varied, with a peak in the third and fourth decades. However, the mean age at presentation in our study (34 years) appeared to be younger than that found in most previous reports (approximately 40 years).[9,12,14,15] The rate of children in our uveitis population (10%) was slightly higher than most estimates from previous studies.[30–32]

Data from referral centres revealed that anterior uveitis was the most common form of uveitis (27.8–63%), followed by posterior (9.3–38%) or panuveitis (7–38%), and intermediate uveitis (4–17%).[33] Chronic uveitis were more common than acute uveitis, and nongranulomatous uveitis occurred more frequently than did granulomatous uveitis. Findings from community-based studies showed a significantly higher rate of anterior uveitis and lower rate of other forms of uveitis.[9,10,12] The frequencies for various forms of uveitis in our study were similar to those of studies from tertiary referral centres,[14,15] while our institution is not exclusively a tertiary referral centre, but also a secondary and primary ophthalmic care centre.

The results of our study showed that for a large proportion of patients (64.8%), a definitive or presumed specific diagnosis was established based on history, including a review of medical systems, a comprehensive ophthalmologic examination, and selected laboratory and ancillary tests. The reported frequency of a systemic

disease or a specific ocular entity underlying uveitis varies from 47.1 to 69.7%.[9,12,15,21,33] The proportion of idiopathic uveitis cases in our series varied, depending on the site of inflammation, from 10.5% in patients with posterior uveitis to 86.3% in patients with intermediate uveitis. Similarly, results of most previous studies showed that the great majority of intermediate uveitis was idiopathic.[33] There was however a large discrepancy between different studies in the proportion of idiopathic cases among other forms of uveitis.[33]

The most common specific diagnoses in our uveitis population were Behçet's disease, herpetic infection, toxoplasmosis, and VKH disease.

Behçet's disease was the most common identifiable specific diagnosis, accounting for 12.3% of all uveitis cases and for 36% of panuveitis in this North African, South Mediterranean series. This finding supports the previous observation of the geographical distribution of Behçet's disease in the old silk route between latitudes 30° and 45° North.[34] A similar high frequency of Behçet's disease as a cause of uveitis has been reported in studies from the Far East, Middle East, and countries around the Mediterranean area.[21,35,36] The well-known strong association of Behçet's disease with HLA-B51 phenotype in these geographic regions suggests the presence of a genetic predisposition to the disease. Behçet's disease is a rare cause of uveitis in most Western countries, where HLA-B51 phenotype is rarely encountered.[5,12]

Herpes simplex infection, presenting as anterior uveitis or keratouveitis, diagnosed based on clinical features, was found to be the next most common cause of uveitis after Behçet's disease in our series. The rate of herpetic uveitis in our patients (11.9%) is high compared to those found in previous reports.[7,9,10,13,17,33] It is unclear if this discrepancy is due to differences in the circulating virus's virulence, background immunity, or prevalence of other predisposing genetic or acquired conditions in the affected populations. Laboratory tests on aqueous humour aspirates, analysing antibodies against viruses HSV or VZV, or detecting viral particles using PCR, might be useful in diagnosing atypical presentations of HSV and VZV infections.[37] Such laboratory tests could not be performed for our patients.

Our results, consistent with those of previous reports,[33] showed that ocular toxoplasmosis was the leading cause of posterior uveitis. The percentage of posterior uveitis attributed to toxoplasmosis in our patients (38.3%) was similar to that reported by others (20–54%). The proportion of uveitis cases attributed to toxoplasmosis was found to be higher in Brazil, and West Africa.[24,38] Diagnosis of ocular toxoplasmosis was based in our patients on typical clinical features with positive toxoplasma serology, completed in any doubtful case with the assessment of intraocular production of antitoxoplasmal antibodies by aqueous humour analysis. Detection of toxoplasma DNA in ocular fluids by PCR, which may contribute to the diagnosis of ocular toxoplasmosis, could not be performed in our patients.

VKH disease, which is known to have a predilection for darkly pigmented races, was in our series the fourth most common occurring type of uveitis (4.4%) and the next most common cause of panuveitis (15%) after Behçet's disease. Results of previous studies showed that VKH disease was more common in Japan and less common in most Western countries.[15,19,35]

Ocular toxoplasmosis, Behçet's disease, and VKH disease, three of the four most frequent causes of uveitis in our series, typically present as posterior uveitis or panuveitis. This could explain the high rate of these two forms of uveitis in our patients. Also, the fact that these three common diseases typically affect young adults may explain the relatively young mean age of our uveitis population.

HLA-B27-positive acute anterior uveitis was not a common type of uveitis in our study, accounting for only 4.4% of all cases. This rate is similar to that observed in studies from USA[15,33] and South European countries,[13] lower than that found in Northern Europe,[10,17] and higher than that reported in studies from Japan.[35] This discrepancy probably reflects racial differences in the frequency of HLA-B27 in the general population.

The results of our study show that sarcoidosis accounted for a small proportion of cases and only three of the eight cases had positive histological examination. Our percentage (1.7%) was similar to that reported in previous studies,[10,12] but lower than that found in others.[15,39] This discrepancy might be explained by racial and geographic factors, and also by a variable difficulty in diagnosing sarcoidosis.

Tuberculosis and syphilis, two classic infectious causes of uveitis, accounted in our series for only 1.1 and 0.6%, respectively, consistent with previous studies.[14,15] However, these two declined infectious diseases are now re-emerging worldwide, particularly because of an increase in the human immunodeficiency virus-infected population.[15]

Five patients in our study (1.1%) had posterior uveitis attributed to Mediterranean spotted fever, an infectious disease endemic in Mediterranean countries that is caused by *R. conorii* infection. Mediterranean spotted fever was found to be commonly associated with symptomatic or more frequently asymptomatic retinal involvement.[40,41] It should be considered in the differential diagnosis of intraocular inflammation in a patient with fever and/or skin rash, living in, or travelling back from an endemic area, especially during spring or summer.

The change of causative pattern of uveitis, with the emergence and identification of new clinical entities in the past two decades, was reflected in our Tunisian uveitis population. Numerous specific entities have been identified in our patients, including multifocal choroiditis and panuveitis, serpiginous choroiditis, punctate inner choroidopathy, multiple evanescent white-dot syndrome, idiopathic acute maculopathy, and birdshot retinochoroidopathy.

Uveitis was found to be a significant cause of visual loss and blindness in developed countries.[1] Our findings, together with those from previous reports from developed and developing countries, revealed in patients with uveitis a significant rate of visual impairment, related to numerous causes, particularly cystoid macular oedema and cataract.

Depending on the anatomic location of the uveitis, numerous aetiologic agents may be encountered in North African patients, but the differential diagnosis should particularly focus on Behçet's disease, herpetic uveitis, toxoplasmosis, and VKH disease.

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