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Review

Uveitis: Autoimmunity… and beyond

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ABSTRACT

Objective: Uveitis is the most common ophthalmological finding in the practice of rheumatology and clinical immunology. The condition is frequently idiopathic but about 60 causes of uveitis have been described. Our aim was to analyze the clinical patterns and etiologies of uveitis in a tertiary referral center.

Methods: The records of 912 consecutive patients referred to the department of internal medicine (Lyon University Hospital, Lyon, France) for the diagnostic work-up of uveitis were examined. Demographic, clinical, anatomical, and etiological features of uveitis were analyzed.

Results: The mean age at onset was 48.8 years; 59.8% of the patients were women and 78.2% were Caucasians. Anterior uveitis was the most common type of uveitis (40.6%), followed by panuveitis (31.7%), posterior (18.75%) and intermediate uveitis (9%). 46.9% of the patients had idiopathic uveitis. The most common etiologies were systemic diseases (37.3%), such as sarcoidosis (17.1%), HLA-B27-related uveitis and/or spondyloarthritis (12.5%), and tuberculosis (7.5%).

Conclusion: We describe one of the largest cohorts of consecutive uveitis patients referred to a department of internal medicine. The high percentage of uveitis associated with underlying (systemic) diseases highlights the need for a multidisciplinary approach, in order to reduce the diagnostic delay.

1. Introduction

Uveitis is defined as an inflammation of the iris, ciliary body, vitreous, retina and/or choroid. Its incidence is 17-52/100,000 person-years while its prevalence is 38–284/100,000 individuals [1–4]. In the USA, a medical insurance claims-based analysis of 4 million individuals reported a prevalence of 133/100,000 persons, with predominantly non-infectious uveitis (90.7%) and anterior uveitis (80%) [5]. About 10–15% of preventable blindness in Western countries is caused by uveitis or its complications. A major vision loss (i.e. best-corrected visual acuity $\leq$20/50) was reported in 20–70% of the patients in uveitis referral centers [6].

About 60 causes of uveitis have been described and can be classified into five groups including pure ophthalmological entities, infectious and inflammatory diseases, masquerade syndromes, and drug-related uveitis. The epidemiology varies depending on genetic and ethnic factors (e.g. HLA-B27, Behcet's disease and sarcoidosis), environmental factors (e.g. tuberculosis), the disease definition (e.g. requirement of a histological proof for sarcoid uveitis), the inclusion of some ophthalmological entities in the idiopathic uveitis group (e.g. pars planitis), the paraclinical investigations that were performed (e.g. nuclear imaging), and the patients' referral (e.g. tertiary centers). Such variability explains the great heterogeneity in epidemiological studies.

The epidemiology also varies according to geographical areas; such as Vogt-Koyanagi-Harada disease (VKH) and sarcoidosis in Japan [7,8], Behcet's disease in the Mediterranean Rim and Asia [9], tuberculosis in India [10], and toxoplasmosis in South America [11,12]. In Western countries, approximately one-quarter of the cases are related to ophthalmological diseases, one-quarter to systemic diseases fulfilling consensual diagnostic criteria, one-quarter to presumed systemic diseases, and one-quarter remain unexplained [13]. According to recent studies from western countries and Japan, 23–44% of uveitis are idiopathic [8,14–25].

Since the beginning of the twenty-first century, there were seven

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studies on the distribution, clinical patterns, and etiologies of uveitis [14–17,25], mostly in ophthalmological centers, in Western Europe. There were few studies in France, with only a large study involving 927 patients with chronic severe uveitis who were referred to a tertiary ophthalmological center, between 1991 and 1996 [15].

The aim of this work was to describe the etiological spectrum, and anatomical patterns of uveitis in a large cohort of consecutive patients referred to our department of internal medicine for the etiological diagnosis of uveitis. Moreover, we analyzed the diagnostic classification according to demographic data and anatomical localization.

2. Patients and methods

2.1. Patients

This study was a retrospective analysis of the records of 1341 patients with “uveitis” referred by the department of ophthalmology (Lyon University Hospital, Lyon, France) or out hospital ophthalmologists to the department of internal medicine (Lyon University Hospital, Lyon, France) between July 2002 and December 2018. The diagnosis of uveitis was always confirmed by an ophthalmological examination. Uveitis related to pure ophthalmological entities, diagnosed by an ophthalmological examination only and referred for the treatment or to rule out differential diagnoses, were excluded (n = 205), as well as uveitis occurring in the course of previously diagnosed diseases (n = 122). According to French law (no. 2004-806, August 9, 2004), this study did not require the research ethics committee approval because data were collected retrospectively and the patients' management was not modified.

2.2. Diagnostic work-up and definitions

All the patients underwent a standard screening protocol for uveitis, which included a tuberculosis skin test, a C-reactive protein and erythrocyte sedimentation rate (ESR), a complete blood cell count (CBC), a serological tests for syphilis, and a chest X-ray [26]. Human leucocyte antigen (HLA)-B27 typing was performed in patients with acute anterior uveitis. In chronic anterior uveitis or granulomatous uveitis, an angiotensin-converting enzyme (ACE) and a chest computerized tomography (CT) scan were performed.

The diagnostic screening for sarcoidosis included conjunctival or skin biopsies if there were clinically suggestive features. Some patients underwent a minor salivary gland biopsy (MSGB), a transbronchial lung biopsy, a bronchoalveolar lavage (BAL), a cerebral magnetic resonance imaging (MRI) or a nuclear imaging. This work-up was completed in some patients by an anterior chamber paracentesis (with a polymerase chain reaction for Herpesvirus, *Toxoplasma* or RNA16S, and sometimes an interleukin-10 measurement), a vitreous biopsy, and/or a lumbar puncture, when appropriate.

The Standardization of Uveitis Nomenclature was used throughout this study for the anatomical classification of uveitis [4,27].

Briefly, the diagnostic criteria used were:

- the international study group for Behcet's disease criteria [28];
- the Levinson's criteria [29] or the global diagnostic criteria for birdshot retinochoroidopathy [30]. All birdshot retinochoroidopathy were HLA-A29 positive;
- the 2010 revised McDonald's criteria for multiple sclerosis (MS) [31] and Okuda's criteria for radiologically isolated syndromes (RIS) [32]. All MS diagnoses or RIS were made in partnership with a neurologist.
- The international criteria for the diagnosis of sarcoidosis [33] (with Zajicek's classification for neurosarcoidosis) [34]. In the absence of histological proof, we used Abad's modified criteria [35]. Patients had presumed sarcoid uveitis if they had at least 2 of the following 4 criteria: typical changes on chest X-ray or CT scan, a predominantly CD4 lymphocytosis on BAL fluid analysis, an elevated ACE or an 18-fluorodeoxyglucose (18-FDG) uptake on scintigraphy. They had indeterminate sarcoid uveitis when only one criterion was met.
- the *Assessment of SpondyloArthritis international Society* (ASAS) criteria for spondyloarthritis [36]. HLA-B27 positive patients with acute non-granulomatous anterior uveitis without clinical and/or radiological features of spondyloarthritis were diagnosed as HLA-B27-related anterior uveitis;
- the revised diagnostic criteria for VKH disease [37];
- Gupta's criteria for the diagnosis of intraocular tuberculosis [38].
- Whenever the intraocular inflammation could not be assigned to a specific diagnosis, the uveitis was considered as *idiopathic*.

2.3. Data collection

We collected patients' demographic data, follow-up times, and the following ophthalmological characteristics at diagnosis: anatomical type of uveitis (anterior, intermediate, posterior, panuveitis) [26] and anterior chamber examination (tonometry, slit lamp, biomicroscopy to assess whether the uveitis was granulomatous or not). We also reported whether the uveitis was acute or chronic, and uni- or bilateral.

2.4. Statistical analysis

Data are described as frequencies and/or percentages for categorical variables and as medians and minimum-maximum ranges for quantitative variables. Most of the time, data were not compared between subgroups because of the great heterogeneity of sample sizes.

All analyses were performed using an R-software, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Demographic data

The department of ophthalmology is a referral center for uveitis in Rhône-Alpes (8.5 million inhabitants). After excluding 102 patients because of insufficient data, 912 patients were included, of which 545 (59.7%) women. 832 patients were actually referred by the department of ophthalmology. Patients' characteristics are shown in Table 1. Overall, the mean age at diagnosis was 48.8 (4–92) years. 199 (21.8%)

Table 1
Characteristics of the 912 patients with uveitis.

Characteristics	n = 912 (%)
Sex, n	
Men	367 (40.3)
Women	545 (59.7)
Mean age at diagnosis (years)	48.8
Ethnicity, n	
Caucasian	713 (78.1)
North-African	144 (15.7)
Sub-Saharan	23 (2.5)
Asian	15 (1.6)
West Indies	7 (0.7)
Others	10 (1.0)
Characteristics of uveitis	
Bilateral, n	537 (58.8)
Chronic, n	608 (64.5)
Non-granulomatous, n	649 (71.1)
Non-hypertensive, n	853 (93.5)
Anatomical type, n	
Anterior	370 (40.6)
Intermediate	82 (9.0)
Posterior	171 (18.7)
Panuveitis	289 (31.7)

Table 2
Etiological distribution of the 912 uveitis.

Etiology	Patients (n)	By subcategory (%)
Idiopathic	428	
Systemic diseases	340	
Sarcoidosis	156	45.8
Histologically-proven sarcoidosis	85	25
HLA-B27-related uveitis	57	16.7
Spondyloarthritis	57	16.7
Behcet's disease	28	8.2
Vogt-Koyanagi-Harada	9	2.6
Multiple Sclerosis[a]	18	5.2
Others[b]	15	4.4
Lymphoma	16	
Ophthalmological entities	21	
Birdshot retinochoroidopathy	15	71.5
Others[c]	6	28.5
Infections	99	
Tuberculosis	68	68.7
Herpesvirus	5	5.0
Toxoplasmosis	2	2.0
Lyme disease	10	10.1
Syphilis	10	10.1
Others[d]	4	4.0
Medication[e]	8	

(SFU, n = 1), sympathetic ophthalmia (n = 1), Idiopathic Retinitis, Vasculitis, Aneurysms and Neuroretinitis (IRVAN, n = 1), idiopathic multifocal choroiditis (n = 2), Fuchs' heterochromic cyclitis (n = 1)

[a] Including 5 radiologically isolated syndrome.

[b] Other systemic diseases: granulomatosis with polyangiitis (n = 2) relapsing polychondritis (n = 1) giant cell arteritis (n = 1), auto-inflammatory syndromes (n = 3), uveo-meningitis (n = 2), common variable immunodeficiency (n = 2), tubulointerstitial nephritis and uveitis (n = 4).

[c] Other pure ophthalmologic entities: unilateral subretinal fibrosis and uveitis syndrome.

[d] Other infections: leptospirosis (n = 1), *Bartonella* (n = 1), endocarditis (n = 1), uveomeningitis (n = 1).

[e] Medications: BCG-therapy (n = 2), immune check-point inhibitors (n = 2), etanercept (n = 2), rifabutine (n = 1), interferon (n = 1).

patients were non-Caucasian, including patients from North Africa (15.7%), Sub-Saharan Africa (2.5%), Asia (1.6%) and the West Indies (0.8%).

3.2. Anatomical diagnosis

The anatomical distribution of uveitis was: anterior uveitis (AU, 40.6%), intermediate uveitis (IU, 9%), posterior uveitis (UP, 18.8%), and panuveitis (PU, 31.7%).

Among the 912 patients, 58.9% had a bilateral disease and 66.7% had a chronic course. Most were non-hypertensive (93.5%) or non-granulomatous (60.3%) (Table 1).

3.3. Etiological diagnosis

A definite etiological diagnosis was made in 484 (53.1%) patients. 37% of uveitis were associated with a definite or presumed systemic diseases, 2.3% were purely ophthalmological entities, 10.8% were of infectious origin, 1.8% were related to a lymphoma and 0.8% were related to drug side effects (Table 2). The most commonly identified systemic diseases were: sarcoidosis (17.1%, n = 156), of which 85 were histologically proven, HLA-B27-related anterior uveitis (6.3%), spondyloarthritis (6.3%), Behcet's disease (3.1%), multiple sclerosis or radiologically isolated syndromes (2%), and VKH disease (1%). Twenty patients were considered as having presumed sarcoid uveitis on the basis of a positive 18-F-FDG PET/CT suggestive of sarcoidosis, 4 had an isolated alveolar lymphocytosis, while 3 patients had a possible neurosarcoidosis. The most common purely ophthalmological entity was birdshot retinochoroidopathy (1.5%). The most common infectious entities were: tuberculosis (7.5%), Lyme disease (1.1%), and syphilis (1.1%).

Table 3
Etiological distribution according to the anatomical type.

Etiology	Anatomical type			
	Anterior	Intermediate	Posterior	Panuveitis
Idiopathic, %	45.9	62.1	50.3	44.9
Systemic diseases, %				
Sarcoidosis	10.8	18.3	11.7	26.9
Proven sarcoidosis	5.6	11	5.3	14.2
HLA-B27-related uveitis	14.6	0	0	1
Spondyloarthritis	14.8	0	0	1
Behcet's disease	0.8	0	5.3	5.5
Vogt-Koyanagi-Harada	0	0	0.6	2.4
Multiple sclerosis	1.1	6.1	1.2	2.4
Others	2.1	0	0.6	2.4
Ophthalmological entities, %				
Birdshot retinochoroidopathy	0	2.4	5.8	0.7
Fuchs uveitis	0.3	0	0	0
Others	0	0	2.3	0.0
Infections, %				
Tuberculosis	5.7	4.8	12.9	7.3
Herpesvirus	1.3	0	0	0
Toxoplasmosis	0	0	0	0.7
Lyme disease	0.3	2.4	2.9	0.6
Syphilis	0	0	2.3	2.1
Other	0	0	0	1.4
Lymphoma, %	0.5	11	1.7	0.6

3.4. Classification by anatomical type

Table 3 shows the etiological diagnoses according to anatomical localization. The most common diagnoses for anterior uveitis were idiopathic (45.9%), spondyloarthritis (14.8%), HLA-B27-related uveitis (14.6%), and sarcoidosis (10.8%). Intermediate uveitis was most commonly idiopathic (62.1%). Sarcoidosis (18.3%), oculocerebral lymphoma (11%) and multiple sclerosis (6.1%) were the most common diseases associated with intermediate uveitis. For posterior uveitis, the most frequent diagnoses were idiopathic (50.3%), tuberculosis (12.4%), sarcoidosis (11.7%) and birdshot retinochoroidopathy (5.8%). For patients with panuveitis, a specific diagnosis could be established in 55.1% of the cases; including sarcoidosis (22.9%), tuberculosis (7.3%), and Behcet's disease (5.5%).

3.5. Uveitis by age, sex, and ethnicity

Within patients with a definite etiology, young patients (aged < 29 years at uveitis onset) had more frequently Behcet's disease, HLA-B27-related anterior uveitis (10.3% each) and spondyloarthritis (8.6%) (Table 4). Between 30 and 59 years old, sarcoidosis was the most frequent etiology (14%), followed by spondyloarthritis (8.6%), tuberculosis (7.5%) and HLA-B27-related anterior uveitis (7%). In patients > 60 years old, sarcoidosis was the most frequent etiology (30.3%) followed by tuberculosis (11%). Sarcoidosis was more frequently histologically proven in patients aged < 60 years (70.1% vs 42%).

The male/female ratio was 0.67 in the whole cohort. Behcet's disease, tuberculosis, and syphilis were more frequent in men, while sarcoidosis tended to be more frequent in women (Table 5).

The etiologies also varied according to ethnicity (Table 6). The most frequent diagnoses in Caucasians were sarcoidosis (17.7%) and HLA-B27-related uveitis (7.1%). In North African patients, the most common etiologies were sarcoidosis (14.5%), tuberculosis (12.4%), spondyloarthritis and Behcet's disease (6.9% each). Sub-Saharan Africans had mostly tuberculosis (34.8%), and sarcoidosis (21.7%).

Table 4
Etiological distribution by age.

Etiology	≤29	Age30–59	> 60
Idiopathic, %	49.4	46	47.1
Systemic diseases, %	44.8	36.5	36
Sarcoidosis	7.5	14	30.3
Proven sarcoidosis	4.6	8.8	12.8
HLA-B27-related uveitis	10.3	7	3.0
Spondyloarthritis	8.6	8.6	1.0
Behcet's disease	10.3	1.8	0.6
Vogt-Koyanagi-Harada	2.3	0.7	0.3
Multiple sclerosis	2.3	2.7	0
Other	2.3	1.8	1.0
Ophthalmological entities, %	1.7	2.7	2
Birdshot retinochoroidopathy	0.6	1.8	2.0
Fuchs	0	0.2	0
Other	1.1	0.7	0
Infectious, %	2.9	11.6	14.1
Tuberculosis	2.3	7.5	11.1
Herpesvirus	0.6	0.4	0.6
Toxoplasmosis	0	0	0.6
Lyme disease	0	1.4	1.3
Syphilis	0.6	1.8	0.3
Other	0	0.4	0.3
Lymphoma, %	0	1.6	3.0

Table 5
Etiological distribution by gender.

Et Etiology	Gender	
	Male	Female
Idiopathic, %	40.3	51.2
Systemic diseases, %		
Sarcoidosis	12.8	17.4
Proven sarcoidosis	6.3	9.7
HLA-B27-related uveitis	7.1	5.7
Spondyloarthritis	6.3	6.4
Behcet's disease	4.6	2.0
Vogt-Koyanagi-Harada	1.4	0.7
Other	1.3	1.8
Ophthalmological entities, %		
Birdshot retinochoroidopathy	2.2	1.3
Fuchs uveitis	0.3	0
Other	0.6	0.6
Infectious, %		
Tuberculosis	10.0	6.2
Herpesvirus	0.6	0.5
Toxoplasmosis	0.3	0.2
Lyme disease	1.6	0.7
Syphilis	2.7	0
Other	0.8	0.2
Lymphoma, %	1.8	1.3

4. Discussion and literature review

This is a large cohort of consecutive uveitis patients referred to a highly specialized department of internal medicine for the etiological diagnosis of uveitis. Several epidemiological studies were conducted worldwide but only a few in departments of rheumatology [17,18]. In Jakob et al. study, 1686 patients with uveitis were included at the Interdisciplinary Uveitis Center of Heidelberg between October 2001 and October 2006. For the diagnosis of associated systemic diseases, a detailed medical history and clinical examination by a rheumatologist were undertaken, and basic blood tests and chest radiographs were performed. In this study, sarcoidosis (4.9%) and ankylosing spondylitis (4.9%) were the most frequent associated systemic diseases. In Lopalco et al. study, 278 patients with non-infectious uveitis were evaluated in two tertiary referral rheumatology departments in Italy [18]. An associated disease was identified in 41.7% of the patients, mostly Behçet's disease, ankylosing spondylitis and juvenile idiopathic arthritis. In our practice, most patients are referred to an internist for the diagnostic work-up of uveitis if there is no obvious diagnosis, such as post-surgical or traumatic uveitis, a previously known disease likely to be the cause of the uveitis and/or a specific ocular diagnosis (diagnosed by ophthalmological examination, such as toxoplasmosis infection, Herpesvirus infection…) [26].

Table 6
Etiological distribution by ethnicity.

Etiology	Ethnicity		
	Caucasian	North-African	Sub-Saharan
Idiopathic, %	47.1	44.8	39.1
Systemic diseases, %			
Sarcoidosis	17.7	14.5	21.8
Proven sarcoidosis	8.8	11.7	13.0
HLA-B27-related uveitis	7.1	4.1	0
Spondyloarthritis	6.3	6.9	0
Behcet's desease	2.5	6.9	4.3
Vogt-Koyanagi-Harada	0.6	2.8	0
Multiple sclerosis	1.8	3.4	0
Other	1.4	1.3	0
Ophthalmological entities %			
Birdshot retinochoroidopaty	2.1	0	0
Fuchs uveitis	0.1	0	0
Other	0.8	0	0
Infectious, %			
Tuberculosis	5.1	12.4	34.7
Herpesvirus	0.7	0	0
Toxoplasmosis	0.4	0	0
Lyme desease	1.4	0	0
Syphilis	1	2.1	0
Other	0.3	0	0
Lymphoma, %	2.2	0	0

In two previous French studies, 34% of uveitis were *unclassified* [15,39]. In the first study, Bodaghi et al. analyzed a series of 927 consecutive patients referred to their department of ophthalmology during 5 years, for the diagnosis and/or therapeutic management of severe uveitis [15]. Hadjadj et al. recently conducted a retrospective study of adult patients referred by the department of Ophthalmology during 6 years (tertiary referral center) to the department of Internal Medicine for the diagnostic work-up of uveitis [40,41]. The ULISSE study (Uveitis cLInical and medicoeconomic evaluation of a Standardized Strategy of the Etiological diagnosis), was performed in 21 French centers and the aim was to assess the efficiency of a standardized diagnostic approach compared to an open strategy. There was an etiological diagnosis in 50.4% of the cases in the standardized group versus 54.4% in the "open strategy" group [26]. As in our work, patients who had a surgery or a trauma, a known pathology likely to be the cause of the uveitis, a specific ocular disease diagnosed by ophthalmic examination only were excluded. Despite progress in diagnostic tests and clinical research, and the development of multidisciplinary specialized departments, the rate of unclassified uveitis remains high (23 to 40% in Western Europe) [14–19,24,27] (Table 7). In this setting, immunotherapeutic interventions have led to significant improvements and studies to evaluate new options are ongoing [42,43]. Basic research should also help understanding the immune mechanisms involved in autoimmune uveitis and lead to the pre-clinical testing of potential new therapies [44].

Compared to recent series in Western Europe, there were less anterior uveitis but more idiopathic uveitis as well as posterior uveitis and panuveitis in our study. The low proportion of uveitis patients with an etiological diagnosis may be explained by the exclusion of specific ocular entities diagnosed by ophthalmological examination only, which were included in other studies. With regards to anatomical distribution, the difference is certainly explained by the referral of patients that

Table 7
Main previous epidemiological studies in Western Europe.

First author	Bodaghi	Cimino	Jakob	Barisani-Asenbauer	Jones	Llorenç	Luca	Our study
Country	France	Italy	Germany	Austria	UK	Spain	Italy	France
Population, n	927	1064	1686	2619	3000	1022	990	912
Uveitis, %								
Anterior	28.5	51.2	45.4	59.9	46.0	52.0	53.5	40.6
Intermediate	15	5.8	22.9	14.8	11.1	9.0	7.5	9
Posterior	21.6	23.4	13.5	18.3	21.8	23.0	16.2	18.75
Panuveitis	35	19.6	6.2	7.0	21.1	15.0	22.8	31.7
Etiology, %								
Idiopathic	34	26	35.3	39.3	31.2	26	23	46.9
Sarcoidosis	6.4	3	4.9	2.4	9.7	3	4.3	17.1
B27 + or SPA	5	7	14	18.3	4.5	10	7.7	12.5
Behcet's disease	6.1	5.3	2.2	1.8	2.7	5	4.8	3
VKH	2	2.5	NA	0.4	0.8	1	4.1	1
Multiple sclerosis	1.7	NA	3.4	1	0.6	0.8	NA	2
Birdshot	4.4	NA	NA	0.4	1.2	3	0.8	1.6
Pars planitis	11.3	NA	NA	NA	NA	1	3.3	NA
Fuchs uveitis	2.7	22.7	8.5	3.4	11.5	1	9.7	0.1
Toxoplasmosis	11.9	6.9	5.1	7.5	6.9	7	4.7	0.2
Tuberculosis	4.1	4.5	NA	NA	3.3	5	5.7	7.5
Herpesvirus	8.2	9.9	6.3	8.6	3.5	12	15.6	0.5
Lyme disease	1.1	NA	1.4	NA	NA	NA	NA	1.1
Syphilis	0.6	NA	NA	NA	0.3	NA	0.8	1.1

B27 +: HLA-B27 positive.
SPA: ankylosing spondylitis.
VKH: Vogt-Koyanagi-Harada disease.
NA: Not Available.

selects more severe uveitis. Thus, the anatomical distribution in our population is close to that of other published series in tertiary referral centers where anterior uveitis accounted for 29–60% of the cases [15,39]. Intermediate uveitis was the less frequent anatomical type (9%), as in previous studies, except for Jakob's (23%) [17]. In our study, intermediate uveitis remained unclassified in 62.1% of the cases, but we excluded pars planitis. Sarcoidosis, primary intraocular lymphoma, multiple sclerosis and tuberculosis were the main etiologies among intermediate uveitis. This is consistent with previous studies [14,16–18,39], except for ocular lymphoma, which was often excluded or considered as a masquerade syndrome in other studies, although in our experience the diagnostic work-up is initially similar to conventional uveitis. There was no Behcet's disease in this subgroup unlike in other larger cohorts in different countries [14,17].

Overall, the most frequent diagnosis in our study was sarcoidosis (45.8% of systemic diseases). The prevalence of sarcoidosis was higher than previously reported in Western European series where it ranged from 2.4–9.7% [8]. Uveitis occurring in the course of previously diagnosed diseases were excluded to avoid a referral center bias. Other factors may have contributed to this difference, such as the diagnostic criteria for sarcoidosis. These criteria vary among studies and a histological proof may be required or not to establish the diagnosis [14,15]. In our series, we used Abad's modified criteria with 18-FDG PET/CT instead of gallium scintigraphy, since it is nowadays considered as superior for the diagnosis of sarcoidosis [45]. The actual IWOS (International Workshop on Ocular Sarcoidosis) criteria were not used, as their relevance was recently questioned. In a recent study, Nisha et al. showed that the IWOS clinical findings and investigational tests had low sensitivities, except for bilateral hilar lymphadenopathy [13]. The high proportion of sarcoidosis in our population may also be explained by the exhaustiveness of investigations, as 20 patients were considered as having sarcoid uveitis on the basis of an positive 18-FDG PET/CT only while 4 patients had an isolated lymphocytic alveolitis [46]. We previously showed that increasing age at diagnosis of uveitis, the presence of posterior synechiae and the positivity of a high-resolution chest CT are associated with 18-FDG PET/CT signs consistent with sarcoidosis [47]. We suppose that there might be a less important hilar or mediastinal involvement in the elderly, that is identified by a chest CT and/or an 18-FDG PET/CT only [48].

HLA-B27-related uveitis and spondyloarthritis were the second most common causes of uveitis (11.4%), as in other studies. This relatively high proportion, despite a low rate of anterior uveitis, may be explained by the systematic HLA typing of patients with anterior uveitis [49]. Moreover, patients with low back pain were systemically investigated for spondyloarthritis. Haroon et al. recently developed a diagnostic algorithm for the early diagnosis of spondyloarthritis in patients presenting with acute anterior uveitis [50]. These criteria were: back pain for > 3 months or arthralgia before 45 years old and (ii) HLA-B27 positivity or psoriasis. This tool (DUET, Dublin Uveitis Evaluation Tool) was 96%-sensitive and 87%-specific for the diagnosis of spondyloarthritis.

The most frequent infection in our patients was tuberculosis, with a higher prevalence than reported in recent Western European series [19], due to interferon-γ releasing assays (IGRA) and a better awareness of 'mimicking' forms of uveitis (including serpiginous-like uveitis) [51].

The frequency of toxoplasmosis and herpesvirus infections was lower in our study than previously reported in Western Europe (Table 7), as these diseases may have been quite easily diagnosed by ophthalmologists, and therefore not included.

The diagnosis was established later on in six patients on the basis of a successful valaciclovir treatment or after a new ophthalmological examination (toxoplasmosis). We recently reported that repeating ophthalmological examinations may be useful in patients with idiopathic uveitis [52].

Birdshot retinochoroidopathy was the most frequent ocular syndrome, with a lower prevalence than in Bodaghi's study [15]. Most of these patients were referred to the department of internal medicine with a suspected sarcoidosis or retinal vasculitis. Several authors consider that HLA-A29 typing may help diagnose atypical cases of birdshot retinochoroidopathy. For Herbort et al., HLA-A29 positivity should be an essential diagnostic criterion, as the association with birdshot retinochoroidopathy might be close to 100% when using PCR testing coupled with indocyanine green angiography. This approach could lead to an earlier diagnosis and treatment, as the pathognomonic birdshot

fundus lesions are probably scar tissue, likely to be missing at disease onset [53]. On the opposite, the absence of HLA-A29, given its strong negative predictive value, should encourage to search for other diagnoses, especially sarcoidosis [54].

Finally, our study confirmed a strong demographical and ethnical burden. The most frequent diagnoses among young and middle-aged adults were Behcet's disease and HLA-B27-related anterior uveitis (10% each), followed by spondyloarthritis (8.6%) and sarcoidosis (7.5%). Our study also confirmed the high prevalence of sarcoid uveitis in patients aged over 60 years presenting with uveitis, especially women.

Tuberculosis and sarcoidosis were frequent in patients from North Africa or from Sub-Saharan Africa. On the other hand, birdshot retinochoroidopathy was only seen in Caucasian patients. In Llorenç et al. series of 1022 patients in Spain, there were similar results with a large variety of etiologies and a strong geographical burden in a multi-ethnic population [16].

The main limit of our study is a selection bias due to the referral of patients who were certainly not completely representative of the general population. Most patients with obvious diagnoses or acute (anterior) uveitis did not require a multidisciplinary approach and were not referred to our department. Thus, our cohort represents a subset of patients with more severe, chronic and complex uveitis. Nevertheless, the large number of cases (912 patients) can counteract, at least in part, this selection bias. Another limit is that > 80% of the patients were Caucasians and our conclusions may not apply outside Western Europe. Finally, the study design was retrospective and some data were missing.

5. Conclusion

This is the largest cohort study of patients with uveitis referred to a department of internal medicine for the diagnostic work-up of uveitis. Despite a huge improvement in the diagnostic strategy, a large number of uveitis remains idiopathic. A multidisciplinary approach, involving the ophthalmologist, the internist and/or the rheumatologist, may increase the diagnostic rate, especially for complex, chronic or severe uveitis.

Declaration of Competing Interest

The authors declare no conflict of interest

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