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**CLINICAL RESEARCH** 

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# A Retrospective Observational Study of Uveitis in a Single Center in Poland with a Review of Findings in Europe

Authors' Contribution: Study Design A Data Collection B Statistical Analysis C Data Interpretation D Manuscript Preparation E Literature Search F Funds Collection G	BCD 2 ABCDEF 3	Mariusz Przybyś	<ol> <li>Department of Ophthalmology, Medical University of Warsaw, Warsaw, Poland</li> <li>Student Research Group (Ophthalmology), Medical University of Warsaw, Warsaw, Poland</li> <li>Department of Infectious Tropical Diseases and Hepatology, Medical University of Warsaw, Warsaw, Poland</li> </ol>
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Material	ackground: //Methods: Results: onclusions:	department of ophthalmology in Poland, and to comother European countries. Review of local patient records between 2005–2015 included age, gender, imaging findings, and laborate publications from 1976–2017 that reported observate analysis compared the findings. Between 2005–2015, 279 patients were diagnosed wincluding unilateral uveitis (60.5%), with posterior unuveitis (12.9%). A general etiology was established in infection (27.9%), and an association with systemic causes of uveitis included toxoplasmosis (17.9%), Fursarcoidosis (6.1%), toxocariasis (6.1%), HLA-B27-assoc rosis (4.7%), ankylosing spondylitis (3.6%) and herper (24,126 patients with uveitis) from 12 European courtis (36.6%); the identified causes included toxoplasmosis	out Europe, the causes of uveitis are varied. Genetic, geo-
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# Background

In Europe, uveitis is one of the main causes of blindness middle-age, affecting 5–10% of individuals [1–4]. Uveitis is a heterogeneous group of inflammatory ocular diseases differing in etiology and anatomical location and includes an inflammatory process that can be caused by a variety of endogenous and exogenous factors [5–8]. Uveitis induced by some topically or systemically administered drugs has been also reported [9–11]. Some types of malignancy may also present with uveitis, which may delay the detection of the underlying cause [12–14].

Due to the variety of causes of uveitis, the diagnosis and treatment require an interdisciplinary approach. There have also been reports of geographical variations in the etiology of uveitis [5,6]. Therefore, the aims of this study were to review the causes, presentation, and clinicopathological associations of uveitis in a retrospective series of patients referred to the Department of Ophthalmology, Medical University of Warsaw, Poland, and to compare the findings with previously published studies from other European countries, to identify the similarities and differences.

# **Material and Methods**

### Patients and study design

The study was conducted according to the guidelines of the Declaration of Helsinki.

All records of patients referred with a presumptive diagnosis of uveitis from the Department of Ophthalmology, the Medical University of Warsaw, between 2005 and 2015 were reviewed. The anatomical classification and diagnosis of uveitis were based on the criteria of the International Uveitis Study Group (IUSG) [15,16].

### **Ophthalmic investigations**

From the review of the clinical records, standard ophthalmic examination was performed in all cases and when required, ocular ultrasonography, fluorescein or indocyanine green angiography, optical coherence tomography (OTC), perimetry, and magnetic resonance imaging (MRI) of the head were performed.

### General clinical and laboratory investigations

All patients had a general medical evaluation, including a chest X-ray, blood pressure measurement, urinalysis, complete blood cell count (CBC) with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) test. Depending on the clinical picture, other tests included genetic tests for the presence of HLA B-27 and HLA A-29, and serological tests for toxoplasmosis, toxocariasis, herpes viruses, borreliosis, bartonellosis, syphilis, and human immunodeficiency virus (HIV) infection. In selected cases, additional investigations were performed, including tests for angiotensin-converting enzyme (ACE), antinuclear antibodies (ANAs), the anti-neutrophil cytoplasmic antibody (ANCA) test, and the QuantiFERON-TB test for infection with *Mycobacterium tuberculosis*. All cases of uveitis from sarcoidosis and tuberculosis were associated with pulmonary disease. Patients with suspected systemic disease were referred to a rheumatologist, pulmonologist, or neurologist and some patients had magnetic resonance imaging (MRI) or lumbar puncture.

### Literature review of cases of uveitis in Europe

Using the Medline database, a review of the literature was performed from 1976–2017 that reported observational data from patients with uveitis in Europe, using the following terms for the literature search: 'uveitis,' 'pattern of uveitis,' 'uveitis in Europe,' and 'epidemiology of uveitis.' Twenty-four articles published in the years 1976–2017, reporting uveitis in 24,126 patients in Europe were identified [19–43]. The records of patients referred to the Department of Ophthalmology and the literature data were analyzed in terms of gender, age, and major causes of uveitis, to identify similarities and differences.

### Statistical analysis

Statistical analysis was performed using STATA/Special Edition version 14.2 (Stata Corp LP, College Station, Texas, USA). The mean ± standard deviation (SD) were used. The frequency of occurrence were expressed as percentages (%). For the contingency tables, the chi-squared ( $\chi^2$ ) test of independence was performed. Multinomial regression analysis was applied to calculate relative risk ratios (RRR) for a selected anatomical localization of uveitis versus all other localizations and by gender. Probabilities of occurrence of a given condition were estimated using logistic regression models. Gender-related differences in the investigated parameters between the groups were tested using the multifactorial analysis of variance (ANOVA) without replication. Fisher's protected least-significant difference (LSD) test for multiple comparisons was performed to detect statistically significant differences between pairs of results. A p-value of <0.05 was considered statistically significant.

# Results

# Retrospective observational study findings (Poland, 2005–2015): Demographic findings for patients with uveitis

Following a review of the clinical records of patients with a presumptive diagnosis of uveitis from the Department

Diagnosis	Overall (n=279)	Women (n=172)	Men (n=107)	RRR *	p-Value
	n (%)	n (%)	n (%)	(95% CI)	
Anterior uveitis	74 (26.5)	38 (22.1)	36 (33.6)	1.79 (1.04–3.06)	=0.035
Intermediate uveitis	36 (12.9)	19 (11.1)	17 (15.9)	1.52 (0.75–3.08)	=0.243
Posterior uveitis	135 (48.4)	88 (51.2)	47 (43.9)	0.69 (0.43–1.12)	=0.240
Panuveitis	34 (12.2)	27 (15.7)	7 (6.5)	0.38 (0.16–0.90)	=0.028
p-value		=0.0	)21 <sup>b</sup>		=0.025ª

Table 1. Final overall diagnosis by gender in the single center retrospective observational study from Poland (2005–2015).

\* A multinomial logistic regression model was fitted, where the relative risk ratios (RRR) and the corresponding confidence intervals (CI) were computed for men versus women within each diagnostic category, versus all other categories;  $\mathbf{a} - \mathbf{a}$  p-value for the joint model was provided.  $\mathbf{b} -$  the chi-squared test of independence was performed for comparison purposes.

 Table 2. Overall patient age (years) and age by gender in the single center retrospective observational study from Poland (2005–2015) (mean ±SD).

Diagnosis	Overall	Women	Men	p-Value*
Anterior uveitis	44.0±16.2	47.1±16.8	40.6±15.1	
Intermediate uveitis	32.1±11.9	33.2±12.7	30.8±11.0	<0.001ª
Posterior uveitis	34.3±13.2	33.9±13.6	35.2±12.5	
Panuveitis	48.7±13.1	49.1±10.9	47.0±20.7	=0.261 <sup>b</sup>
	38.3±15.3	39.1±15.3	37.1±15.4	

\*A factorial analysis of variance (ANOVA) was performed; dependent variables were: a – diagnosis, b – gender.

of Ophthalmology, the Medical University of Warsaw, between 2005 and 2015 identified 282 adult patients (Caucasian), including 174 women (61.7%) and 108 men (38.7%). A total of 279 patients were included in the final analysis, 172 women (61.6%) and 107 men (38.3%). Three patients were excluded for the following reasons. Two sisters were ultimately diagnosed with transthyretin amyloidosis masquerading as posterior uveitis [44]. A 42-year-old man was diagnosed with primary intraocular lymphoma, confirmed by vitreous biopsy and flow cytometry.

Of the 279 patients reviewed, anterior uveitis was diagnosed in 26.5% (22.1% women vs. 33.6% men), intermediate uveitis in 12.9% (11.1% women vs. 15.9% men), posterior uveitis in 48.4% (51.2% women vs. 43.9% men), and panuveitis in 12.2% (15.7% women vs. 6.5% men). The gender differences were statistically significant ( $\chi^2$ =9.769; df=3; p=0.021). Anterior uveitis was found to affect men more frequently than women (RRR=1.79; 95% CI, 1.04–3.06; p=0.035); panuveitis was less prevalent among men (RRR=0.38; 95% CI, 0.16–0.90; p=0.028) (Table 1).

The mean age of the 279 patients reviewed was  $38.3\pm15.3$  years. There were no statistically significant differences in

patient age by gender by analysis of variance (ANOVA) (F=1.031; df=1. 274; p=0.261. However, age was significantly associated with differences in diagnosis (F=16.342; df=3. 274; p<0.001). The highest mean age was for subjects with panuveitis (48.7±13.1 years) and the lowest mean age was found for patients with intermediate uveitis (32.1±11.9 years). Fisher's test of least-significant difference (LSD) for multiple comparisons showed that the mean age differed significantly between patients with anterior uveitis compared with intermediate uveitis (p<0.001); anterior uveitis compared with posterior uveitis (p<0.001), and posterior uveitis compared with panuveitis (p<0.001), and posterior uveitis compared with panuveitis (p<0.001) (Table 2). Unilateral presentation of uveitis was found in 60.5% (n=169) and a bilateral presentation.

# Retrospective observational study findings (Poland, 2005–2015): Anatomical and etiological distribution of uveitis

The etiology of uveitis was established in 76.4% (n=213) of all cases in the retrospective study. The main cause of inflammation of the uveal tract was not established in 23.6% (n=66)

	Idiopathic	Toxoplasmosis	Fuchs uveitis	White dot syndromes	Toxocariasis	Sarcoidosis	HLA B-27 AAU	Multiple sclerosis	Ankylosing spondylitis	Viruses	RIS	Rheumatoid arthritis	IRVAN	Tuberculosis	Reiter syndrome	Juvenile idiopathic arthritis	Ulcerative Colitis	Hepatitis C	Boreliosis
Anterior	9 (12)	0	34 (45.9)	0	0	2 (2.7)	16 (21.6)	1 (1.35)	8 (10.8)	0	0	1 (1.35)	0	0	1 (1.35)	1 (1.35)	1 (1.35)	0	0
Intermediate	24 (66.6)	0	0	0	0	4 (11)	0	4 (11)	0	0	3 (8.3)	0	0	0	0	0	0	1	0
Posterior	23 (16.6)	48 (35.5)	0	29 (21)	16 (11.8)	4 (2.96)	0	0	0	6 (4.3)	1 (0.7)	1 (0.74)	4 (2.9)	2 (0.7)	0	0	0	0	1
Panuveitis	10 (29.4)	2 (5.6)	0	0	1 (2.8)	7 (20.6)	0	8 (23.5)	2 (5.6)	1 (2.1)	1 (2.9)	2 (5.6)	0	0	0	0	0	0	0
Total No. (%)	66 (23.7)	50 (17.9)	34 (12.2)	29 (10.4)	17 (6.1)	17 (6.1)	16 (5.7)	13 (4.7)	10 (3,6)	7 (2.5)	5 (1.8)	4 (1.4)	4 (1.4)	2 (1.5)	1 (0.36)	1 (0.36)	1 (0.36)	1 (0.36)	1 (0.36)

 Table 3. Distribution of final diagnoses by anatomical classification in the single center retrospective observational study from Poland (2005–2015) (number of patients, %).

HLA-B27 AAU – HLA-B27 associated acute anterior uveitis (AAU) without systemic disease; RIS – radiologically isolated syndrome, or demyelinating changes on magnetic resonance imaging (MRI) without clinical signs of multiple sclerosis [17]; WDS – white dot syndrome, a group of inflammatory disorders that affect the outer retinal layers, retinal pigment epithelium (RPE) and/or choroid [18]; IRVAN – idiopathic retinal vasculitis, aneurysms, and neuroretinitis.

despite evaluation by other medical specialists and additional investigations. The distribution of the final diagnosis of uveitis, by anatomical classification, is shown in Table 3.

Fuchs uveitis was the most common cause of anterior uveitis (45.9%); most intermediate uveitis (66.6%) and panuveitis (29.4%) was idiopathic; toxoplasmosis was the most frequent cause of posterior uveitis (35.5%). Posterior uveitis was the most common anatomical diagnosis in 135 patients (48.4%), followed by anterior uveitis in 74 patients (26.5%), intermediate uveitis in 36 patients (12.9%), and panuveitis in 34 patients (12.2%). Overall, the etiology of uveitis was ocular-specific (30.1%), infectious (28%), systemic non-infectious (16.5%) and idiopathic (23.6%). The highest percentage of uveitis with unspecified etiology (unclassified) was found in patients with intermediate uveitis and panuveitis (66.6% and 29.4% respectively). Infection was diagnosed in 54% of posterior uveitis cases and systemic immune-mediated disorders were commonly associated with panuveitis (55.8%).

In the 279 patients included in the retrospective review, the most frequent cause of uveitis was Fuchs uveitis (12.2%), toxoplasmosis (17.9%) and white dot syndromes (WDS) (10.4%). The WDS group of 29 patients included cases of multifocal choroiditis, punctate inner choroidopathy, acute posterior placoid pigment epitheliopathy, birdshot chorioretinopathy, subretinal fibrosis and uveitis, serpiginous choroiditis, multiple evanescent white dot syndrome, and acute annular outer retinopathy. Sarcoidosis (6.0%) and multiple sclerosis (4.7%) were the two systemic diseases most frequently identified in patients with uveitis at our center in Poland.

Table 4 summarizes the overall leading causes of uveitis, and the causes by gender. Apart from idiopathic inflammation, the most prevalent causes were toxoplasmosis (17.9%), Fuchs uveitis (12.2%), and WDS (10.4%). Significant differences between male and female patients were found for toxocariasis, toxoplasmosis and for HLA-B27-associated acute anterior uveitis (AAU).

Significant associations were found between the causes of uveitis and patient age for Fuchs uveitis, WDS, toxocariasis, and toxoplasmosis. In summary, the findings from the retrospective review of cases of uveitis from our department in Poland showed that an increase in the patient age by one year favored the occurrence of Fuchs uveitis and sarcoidosis, while a decrease in age by one year reduced the occurrence of WDS, toxocariasis, and toxoplasmosis (Table 5). Table 6 shows the pattern of uveitis associated with the eye segments involved. The most common cause for anterior uveitis was Fuchs uveitis; the most common cause for intermediate and panuveitis was idiopathic inflammation; the most common cause for posterior uveitis was WDS.

Diamania	Overall	Women	Men	Logistic regression estimat	
Diagnosis	n (%)	n (%)	n (%)	OR 95% CI	p-Value*
Idiopathic inflammation	66 (23.7)	42 (24.4)	24 (22.4)	0.89 0.50–1.59	0.704
Fuchs uveitis	34 (12.2)	17 (9.9)	17 (15.9)	1.72 0.84–3.54	4 0.139
Multiple sclerosis	13 (4.7)	10 (5.8)	3 (2.8)	0.47 0.13–1.74	4 0.257
White dot syndrome	29 (10.4)	19 (11.1)	10 (9.4)	0.83 0.37–1.86	5 0.651
Sarcoidosis	17 (6.1)	13 (7.6)	4 (3.7)	0.47 0.15–1.50	0.204
Toxocariasis	17 (6.1)	6 (3.5)	11 (10.3)	3.17 1.14-8.84	0.028
Toxoplasmosis	50 (17.9)	39 (22.7)	11 (10.3)	0.39 0.19–0.80	0.010
Viral aetiology	8 (2.9)	3 (1.7)	5 (4.7)	2.76 0.65–11.80	0.170
HLA-B27 AAU	16 (5.7)	6 (3.5)	10 (9.4)	2.85 1.01-8.09	9 0.049
Ankylosing spondylitis	10 (3.6)	5 (2.9)	5 (4.7)	1.64 0.46–5.80	) 0.445

 Table 4. The overall leading causes of uveitis and causes by gender in the single center retrospective observational study from Poland (2005–2015).

\* Logistic regression models were fitted. OR – odds ratio; CI – confidence interval; HLA-B27 AAU – HLA-B27 associated with acute anterior uveitis (AAU) without systemic disease.

 Table 5. Leading causes of uveitis by patient age (years) in the single center retrospective observational study from Poland (2005–2015) (mean ±SD).

Diagnosis	Present	Absent	Logistic regre	ession estimates	- \/-l*
Diagnosis	Age (years)	Age (years)	OR	95% CI	p-Value*
Idiopathic inflammation	42.5±17.0	37.1±14.2	1.02	1.01-1.04	0.011
Fuchs uveitis	45.1±14.3	37.4±14.9	1.03	1.01–1.06	0.004
Multiple sclerosis	39.4±11.1	38.3±15.2	1.00	0.98–1.03	0.798
White dot syndromes	32.5±11.2	39.0±15.3	0.97	0.94–0.99	0.027
Sarcoidosis	47.6±13.0	37.7±15.0	1.04	1.01–1.06	0.002
Toxocariasis	29.8±11.9	38.9±15.1	0.95	0.90–0.99	0.024
Toxoplasmosis	30.9±10.2	40.0±15.4	0.95	0.92–0.97	<0.001
Viral infections	36.8±19.3	38.4±14.9	0.99	0.93–1.06	0.866
HLA-B27 AAU	36.3±16.1	38.5±15.0	0.99	0.95–1.03	0.677
Ankylosing spondylitis	37.8±12.2	38.4±15.1	1.00	0.96–1.03	0.933

\* Logistic regression models were fitted. Odds ratios (ORs) and corresponding confidence intervals (Cis) refer to the odds in favour of selected causes being diagnosed. The ORs were controlled for gender.

# Comparison of the retrospective observational study findings (Poland, 2005–2015) with the findings from the literature review of uveitis in Europe (1976–2017)

The results of the comparison of data between the retrospective study findings from our center in Poland between 2005–2015, and those from the literature review of findings in other European countries between 1976–2017 are shown in Tables 7–14. The literature review obtained data from 26 published studies (24,126 patients with uveitis) from 12 European countries, ranging from 120 cases in Finland in 1977, to 3,000 cases in the U.K. in 2015 [19–43]. The data were extracted from the 26 published studies and covered a period of 41 years, from 1976–2017. In eight out of the 26 studies the authors did

Discresia	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	
Diagnosis	n (%)	n (%)	n (%)	n (%)	p-Value*
Idiopathic inflammation	9 (12.2)	24 (66.7)	23 (17.0)	10 (29.4)	<0.001
Fuchs uveitis	34 (45.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Multiple sclerosis	1 (1.4)	4 (11.1)	0 (0.0)	8 (23.5)	
White dot syndrome	0 (0.0)	0 (0.0)	29 (21.3)	0 (0.0)	
Sarcoidosis	2 (2.7)	4 (11.1)	4 (2.9)	7 (20.6)	=0.002
Toxocariasis	0 (0.0)	0 (0.0)	16 (11.8)	1 (2.8)	
Toxoplasmosis	0 (0.0)	0 (0.0)	48 (35.3)	2 (5.6)	
Viral infection	0 (0.0)	1 (2.8)	7 (5.2)	1 (2.8)	
HLA-B27 AAU	16 (21.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Ankylosing spondylitis	7 (9.5)	0 (0.0)	0 (0.0)	3 (8.3)	

 Table 6. Diseases (causes) most frequently associated with uveitis by anatomical localization in the single center retrospective observational study from Poland (2005–2015).

\* Some p-values are not provided due to the data separation, or excess of frequencies of zero.

not provide information about the nationality of the subjects. Another eight studies were carried out in ethnically uniform populations of a given country, and in nine studies the subjects came from multinational (multiethnic) populations. In 10 studies, the age range was not specified. Pediatric patients were included in 12 studies. The mean age of all reported patients was 40.4 years (range, 30.7–47.9 years). Women accounted for 52.3% of all patients (range, 42.5–61.6%). The published studies included in the literature review and the demographic characteristics of the study participants are summarized in Tables 7 and 8.

Tables 9–14 summarize the etiology of uveitis in patients from selected studies published between 1976–2017. No obvious patterns could be observed, although non-infectious uveitis syndromes associated with systemic disease were the most prevalent in most European countries. Overall, the findings from the retrospective study performed at our center in Poland between 2005–2015 did not differ significantly from those in other European countries, but in our series of patients, ocular-specific syndromes were the most common (31.8% of all uveitis cases) and uveitis associated with systemic non-infectious disease were the least common (16.8%).

No consistent trends were observed regarding the anatomical localization of uveitis reported from the European studies between 1976–2017 (Table 8), even when including and excluding our own department's observations from 2005–2015. During the 41 years covered by the literature review in Europe (1976–2017), the most common anatomical localization of uveitis reported was anterior, with the mean rate from all studies being 55.2%, ranging from 0.0% in Belgium (in 1999) to 92.2% in Finland (in 1994) [28,32]. In our review from our department in Poland between 2005–2015, posterior uveitis was the most common location in 48.4% of cases, compared with the mean of 21.1% from the remaining European centers (from 1976–2017). Intermediate uveitis was the most common location in 12.9% of cases, compared with the mean of 9.0% from the remaining European centers (from 1976–2017). Panuveitis was the most common location in 12.2% of cases, compared with the mean of 14.9% from the remaining European centers (from 1976–2017).

Toxoplasmosis was diagnosed in 17.9% of all uveitis cases and was present in 35.5% of patients with posterior uveitis, whereas Fuchs uveitis was identified in 12.2% of all uveitis cases and was present in 45.9% of anterior uveitis cases. The WDS cases were associated with 10.4% of all cases, and with 21.5% of posterior uveitis cases. Uveitis from sarcoidosis was present in 6.1% of all cases, and in 11% of cases of intermediate uveitis, 2.9% of posterior uveitis, 2.7% of anterior uveitis, and 20.6% of panuveitis. Infection with *Toxocara* was related to 6.1% of all cases 11.8% of cases of posterior uveitis and 2.9% of cases of panuveitis. HLA B27 AAU was detected in 5.7% of all uveitis patients and 21.6% of patients with anterior uveitis. Multiple sclerosis was diagnosed in 4.7% of all patients and in 23.5% of panuveitis cases, 11.1% of intermediate uveitis cases, and 1.4% of anterior uveitis cases.

Regarding the etiology of uveitis, when the anatomical location was not considered (Table 13), idiopathic uveitis was diagnosed in 36.3% of the patients in our series in Poland (2005–2015), without noticeable deviations from the pooled mean rate from other European centers. Fuchs uveitis was diagnosed in 6.1% of patients in studies from other European countries,

Country	First author	Year of publication	Patient nationality	Gender (% of women)	Mean age (years)	Pediatric patients included	Number of subjects
UK	James	1976					368
Finland	Miettinen	1977	Finnish				120
The Netherlands	Kijlstra	1987	Dutch				1309
Portugal	Palmares	1990	Multiethnic	54.8	36.0		450
The Netherlands	Rothova	1992	Multiethnic	50.0	42.0	Yes	865
The Netherlands	Baarsma	1992					767
Italy	Latanza	1993					369
The Netherlands	Smit	1993	Dutch	52.0		No	750
Switzerland	Tran	1994	Swiss	42.5	43.0	Yes	435
UK	Thean	1996	Multiethnic	48.0	39.2	Yes	712
Italy	Pivetti-Pezzi	1996		53.0	30.7		1417
Finland	Päivönsalo- Hietanen	1997		49.0			1122
Belgium	Levecq	1999			36.5		201
France	Bodaghi	2001	Multiethnic		37.1	No	927
Italy	Mercanti	2001	Italian	48.0	44.4	Yes	655
Poland	Biziorek	2001	Polish	53.3	40.4	Yes	563
Germany	Jakob	2009		57.0		Yes	1916
Italy	Cimino	2010	Multiethnic	54.8	41.0	Yes	1064
UK	Jones	2015	Multiethnic	54.1	45.0	Yes	3000
Spain	Llorenç	2015	Multiethnic	54.0	45.0	Yes	1022
Germany	Grajewski	2015	Multiethnic	55.0		Yes	474
Austria	Barisani- Asenbauer	2015		52.0	38.8	Yes	2619
Spain	Fanlo	2017	Multiethnic	50.0	47.9	No	500
Poland	our observation	2018	Polish	61.7	38.3	No	282

Table 7. Demographic of patients diagnosed with uveitis in published studies from Europe (1976–2017).

Empty boxes: data not available.

which means that in our center, this rate was higher (12.2%). Ankylosing spondylitis was diagnosed in 8.2% of cases overall (3.6% in Poland between 2005–2015 compared with 8.7% in the other European centers between 1976–2017). Sarcoidosis was associated with 4.7% of cases of uveitis overall (6.5% in Poland between 2005–2015 compared with 4.7% in the other European centers between 1976–2017). Multiple sclerosis was diagnosed in 1.7% of cases overall (4.7% in Poland between 2005–2015 compared with 1.3% in the other European centers between 1976–2017). Toxoplasmosis was associated with 9.9% of uveitis cases overall (17.9% in Poland between 2005–2015 compared with 9.4% in the other European centers between 1976–2017) Toxocariasis was detected in 1.4% of all uveitis patients (6.0% in Poland between 2005–2015 compared with 0.5% in the other European centers between 1976–2017). Reiter's syndrome was diagnosed in 1.3% of uveitis patients overall (0.35% in Poland between 2005–2015 compared with 1.4% in the other European centers between 1976–2017). Tuberculosis was the underlying cause in 2.2% of all patients (0.7% in Poland between 2005–2015 compared with 2.3% in

Country	First author	Year of publication	Anterior uveitis (%)	Intermediate uveitis (%)	Posterior uveitis (%)	Panuveitis (%)
UK	James	1976	58.0	0.0	18.0	24.0
Finland	Miettinen	1977	87.5	0.0	8.3	4.1
The Netherlands	Kijlstra	1987				
Portugal	Palmares	1990	60.0	4.0	24.0	12.0
The Netherlands	Rothova	1992	54.5	9.0	16.5	20.0
The Netherlands	Baarsma	1992	50.7	11.3	23.1	14.8
Italy	Latanza	1993	52.0	15.2	28.0	24.0
The Netherlands	Smit	1993	52.0	9.0	24.0	15.0
Switzerland	Tran	1994	62.0	11.0	20.0	7.0
Finland	Päivönsalo- Hietanen	1994	92.2	1.3	5.7	0.8
UK	Thean	1996				
Italy	Pivetti-Pezzi	1996	49.1	12.4	22.1	16.4
Belgium	Levecq	1999	0.0	14.4	49.1	35.8
France	Bodaghi	2001	28.5	15.0	21.5	35.0
Italy	Mercanti	2001	58.0	2.9	26.1	12.9
Poland	Biziorek	2001	44.6	7.3	33.0	15.1
Germany	Jakob	2009	45.4	22.9	13.5	6.2
Italy	Cimino	2010	51.2	5.8	23.4	19.6
UK	Jones	2015	46.0	11.1	21.8	21.1
Spain	Llorenç	2015	52.0	9.0	23.0	15.0
Germany	Grajewski	2015	53.0	19.0	21.0	7.0
Austria	Barisani- Asenbauer	2015	59.9	14.8	18.3	7.0
Spain	Fanlo	2017	65.4	1.8	17.6	15.2
Poland	Retrospective observational study in Poland, 2005-2015	2005–2015	26.5	12.9	48.3	12.2

#### Table 8. Classification of uveitis by anatomical localization in studies from Europe (1976–2017).

Empty boxes: data not available.

the other European centers between 1976–2017). Juvenile rheumatoid arthritis was diagnosed in 2.1% of all patients (0.4% in Poland between 2005–2015 compared with 2.4% in the other European centers between 1976–2017). WDS cases were present in 7.7% of all patients (10.4% in Poland between 2005–2015 compared with 7.2% in the other European centers

between 1976–2017). Viral infections, mainly Herpes viruses, were found in 7.0% of all patients (2.5% in Poland between 2005–2015 compared with 7.2% in the other European centers between 1976–2017).

Author/ Country/Year	ldiopathic	Fuchs uveitis	HLA-B27 AAU	Ankylosing spondylitis	Sarcoidosis	Reiter syndrome	Multiple Sclerosis	Juvenile Idiopathic Arthritis	Rheumatoid Arthritis	Ulcerative colitis	Viral infection	Tuberculosis
Miettinen et al./Finland/1977	86.7	0.0	<b>.</b> 00						~		<b>&gt;</b> 1.9	⊢ 1.0
Rothova et al./The Netherlands/1992	33.0	11.3		9.0	5.0*			2.0			5.1	1.3
Smit et al./The Netherlands/1993	42.0	20.0		14.0	2.0*	1.0		3.0			1.0	
Tran et al./Switzerland/1994		10.0				1.8					15.0	
Pivetti-Pezzi et al./Italy/1996	59.9	17.0									18.9	6.3
Thean et al./UK/1996		17.2										
Bodaghi et al./France/2001	13.6	9.5			6.8		0.4	9.5			31.0	4.9
Mercanti et al./Italy/2001	58.0	17.0			0.0			2.9	2.3		11.2	6.3
Biziorek et al./Poland/2001	67.3											
Jakob et al./Germany/2009	25.0	15.0									8.0	
Cimino et al./Italy/2010	20.0	45.0									19.0	
Jones/UK/2015		25.0								1.3		
Llorenç et al./Spain/2015	36.0	3.0	10.0	10.0	0.7	0.9	0.1	3.0	0.7		20.0	1.0
Grajewski et al./Germany/2015	44.0	7.0	19.0	0.0	11.0	0.0	0.4	4.0	0.0	0.4	12.0	0.0
Barisani-Asenbauer et al./ Austria/2015		4.5	30.5		2.1			3.4		1.0*	11.4	
Fanlo et al./Spain/2017	31.2	4.6	4.2	16.5								
Retrospective observational study in Poland, 2005–2015	12.2	45.9	21.6	11.0	2.7	2.7	1.35	1.35	1.35	1.35	0.0	0.0
Mean prevalence in Europe (own data not included)	43.0	13.7	16.0	9.9	4.0	0.9	0.3	4.0	1.0	0.85	13.0	3.0
Mean prevalence in Europe (own data included)	40.0	15.7	17.0	10.0	3.8	1.3	0.6	3.6	1.0	1.0	12.0	2.6

 Table 9. Etiologic distribution of anterior uveitis from the single center retrospective observational study from Poland (2005–2015) and in other studies from Europe (1976–2017) (% of all uveitis cases reported).

HLA-B27 AAU – HLA-B27 associated acute anterior uveitis (AAU) without systemic disease. Empty boxes: data not available. \* Suspected diagnosis.

# Discussion

Although there have been several published epidemiological studies on uveitis conducted in Europe during the past few decades, there has been only one previously published study conducted in Poland, in 2001 [35]. Therefore, the aim of this study was to review the causes, presentation, and clinicopathological associations of uveitis in our department of ophthalmology in Warsaw, Poland, between 2005–2015, and to compare the findings with previously published studies conducted in Europe between 1976–2017

In previously published European studies on uveitis, published between 1976–2017, more patients were included than in our series. This finding is likely due to the fact that in Warsaw there are two tertiary centers for referral of patients with uveitis, while mild cases of uveitis might be treated in private practice [48]. The main difference in the results found between the present retrospective study and previously published European studies was found to be the most common anatomical localization of inflammation. In many European countries, anterior uveitis was found to be the most common form, accounting for 50–60% of all cases, while in study posterior uveitis was

Author/Country/Year	Idiopathic	Multiple Sclerosis	Sarcoidosis	RIS	Hepatitis C	Tuberculosis	Boreliosis
Palmares et al./Portugal/1990	100.0						
Rothova et al./The Netherlands/1992	84.0	5.0	9.0*				
Smit et al./The Netherlands/1993	69.0		16.0*			7.0*	
Tran et al./Switzerland/1994	34.0					2.0	2.0
Bodaghi et al./France/2001	75.5	10.8	2.9			1.4	2.9
Mercanti et al./Italy/2001	36.8		0.0				
Llorenç et al./Spain/2015	38.0	7.0	5.0			6.0	
Grajewski et al./Germany/2015	69.0	9.0	18.0	0.0	0.0	0.0	0.0
Barisani-Asenbauer et al./Austria/2015	75.0	4.9	1.5				
Retrospective observational study in Poland, 2005–2015	66.6	11.0	11.0	8.3	2.7	0.0	0.0
Mean prevalence in Europe (own data not included)	64.6	7.0	5.5			3.1	2.4
Mean prevalence in Europe (own data included)	64.8	7.8	6.4			2.3	1.6

 Table 10. Etiologic distribution of intermediate uveitis from the single center retrospective observational study from Poland (2005–2015) and in published studies from Europe (1976–2017) (% of all uveitis cases reported).

\* Suspected diagnosis. RIS, radiologically isolated syndrome. Empty boxes: data not available.

more prevalent [45–47]. The lower prevalence of anterior uveitis in our series may be explained by the fact that patients might have received treatment in smaller hospitals or private practice, and the increasingly frequent use of biologics in systemic autoimmune diseases has significantly reduced the occurrence of ocular complications.

The second main difference between the findings of our study, conducted in a single center in Poland between 2005–2015, compared with the previously published studies in Europe between 1976–2017, was our finding of a cause of uveitis in 77%. The literature review showed that during the past few decades, the rate of idiopathic uveitis has been decreasing, which is associated with advances in clinical diagnosis, including molecular diagnostic techniques [21,22,25,34,40].

The main manifestations of uveitis observed from review at our center in Poland were ocular-specific (31.8%), infectious (27.9%) and associated with the underlying systemic non-infectious disease (16.8%), while 23.6% of all uveitis cases were unclassifiable. The prevalence of ocular- specific disease from our center in Poland was similar to that observed in Germany (34.3%) but was less than that diagnosed in France, Spain, and Austria [33,36,39,41,42]. Infectious symptoms of uveitis observed from our center in Poland were found at a similar rate to those in France, but were reported less frequently in Germany, Austria, and Spain [33,36,39,41,42]. The prevalence of systemic non-infectious disease from our center in Poland was the lower when compared with previously published studies from other European countries [33,36,39,40–42].

The main causes of uveitis in our department of ophthalmology in Warsaw, Poland, between 2005–2015 were Fuchs uveitis, toxoplasmosis, and the white dot syndrome (WDS), while in other European countries toxoplasmosis, ankylosing spondylitis, and HLA B-27 associated anterior uveitis (AAU) predominated [19,21–23,25,27,32,34,40–42]. The prevalence of ocular toxoplasmosis in our series was similar to that in other European countries. Toxoplasmosis is a major cause of posterior uveitis, and the differences in the occurrence and clinical presentation depend on the time of infection (congenital versus acquired), the prevailing regional strains of the parasite, nutritional habits, host immune status, socio-economic conditions, and climate [45–47,49–57].

In our series, toxocariasis as a cause of uveitis was reported to be higher, than in cases reported in previous European studies [58–60]. The seroprevalence of toxocariasis in Poland depends on the method of testing, the population groups, and the region, ranging from 5% in the Poznań region to 75.6% in Warsaw, which may explain such a high percentage of patients with ocular larva migrans (OLM) in patients with 

 Table 11. Etiologic distribution of posterior uveitis in the single center retrospective observational study from Poland (2005–2015) and in published studies from Europe (1976–2017) (% of all uveitis cases reported).

Author/Country/Year	Idiopathic	Toxoplasmosis	White dot syndrome	Toxocariasis	Viral infection	IRVAN	Sarcoidosis	Tuberculosis	Boreliosis	RIS	Rheumatoid arthritis
Miettinen et al./Finland/1977	50.0	40.0		0.0				10.0			
Kijlstraet al./The Netherlands/1987			1.6								
Rothova et al./The Netherlands/1992	25.0	49.0		0.7	5.6		9.0*	1.0*			
Smit et al./The Netherlands/1993	28.0	42.0	10.0	2.0	4.0						
Tran et al./Switzerland/1994	18.0	42.0	4.5		4.0		13.0				
Pivetti-Pezzi et al./Italy/1996	21.1	60.2		0.0							
Levecq L et al./UK/1996	17.0	39.0		1.0	4.0			0.0			
Bodaghi et al./France/2001	16.5	39.0					1.5	0.5			
Mercanti et al./Italy/2001	21.0	60.2		3.2	2.9		1.2	7.0			
Jakob et al./Germany/2009	29.0	25.0									
Jones/UK/2015		6.9									
Llorenç et al./Spain/2015	7.0	24.0	30.0		7.0		2.0	11.0			
Grajewski et al./Germany/2015	6.0	34.0	37.0	0.0	9.0		2.0	0.0	1.0		
Barisani-Asenbauer et al./Austria/2015	21.9	29.0		1.4			2.5				
Fanlo et al./Spain/2017			25.0								
Retrospective observational study in Poland, 2005–2015	17.0	35.5	21.5	11.8	4.4	3	2.96	1.5	1.0	0.8	0.74
Mean prevalence in Europe (own data not included)	21.7	37.7	18.0	0.9	4.0		3.7	4.0	1.0		
Mean prevalence in Europe (own data included)	21.3	37.5	18.5	2.1	4.0		3.7	3.7	1.0		

\* Suspected diagnosis. RIS – radiologically isolated syndrome; IRVAN – idiopathic retinal vasculitis, aneurysms, and neuroretinitis. Empty boxes: data not available.

uveitis referred to our department [58–60]. Ocular larva migrans (OLM), or ocular toxocariasis, which is the ocular form of the larva migrans syndrome, is due to infection with *Toxocara canis*. For many years the number of pet dogs in Poland has been increasing. Based on the number of rabies vaccination certificates, it is now estimated at 7.5 million (one dog per five people) means that Poland has one of the largest dog populations in Europe [61]. Dog feces in the street dry and particles may be inhaled into the bronchial tree and swallowed causing parasite infestation, a mechanism that may explain very high seroprevalence of toxocariasis in urban adults in Poland [62]. Review of previously published studies has shown that tuberculosis is one of the most common causes of uveitis in Europe, predominantly in the Netherlands, UK, and Spain [21–3,38,39]. In our review of cases in our department in Poland, two cases of uveitis were found in patients with a history of tuberculous pneumonia. The incidence of tuberculosis in Poland decreased from 128.5 per 100,000 in 1970 to 19.1 per 100,000 in 2010 [63,64]. The Polish tuberculosis control program has been developed continuously since the 1920s. In addition to mass vaccination with Bacillus Calmette-Guérin (BCG), there is a free but compulsory treatment of the disease, which also includes quite an aggressive family chemoprophylaxis [63,64].

Table 12. Etiologic distribution of panuveitis in the single center retrospective observational study from Poland (2005–2015) and in
published studies from Europe (1976–2017) (% of all uveitis cases reported).

Author/Country/Year	Idiopathic	Multiple sclerosis	Sarcoidosis	Ankylosisng spodylitis	Toxoplasmosis	Rheumatoid arthritis	Toxocariasis	Viral infection	RIS	Tuberculosis	Boreliosis
Miettinen et al./Finland/1977	20.0		0.0		60.0						
Palmares et al./Portugal/1990			20.0*								
Rothova et al./The Nederlands/1992	27.0		19.0*		8.0			5.0		2.0*	
Smit et al./The Netherlands/1993	39.0		20.0*							9.0*	
Tran et al./Switzerland/1994	35.0		19.0		6.0		3.0	23.0			
Pivetti-Pezzi et al./Italy/1996	32.0		3.5		15.3						
Levecq L et al./UK/1996	33.3		12.5		13.9						
Bodaghi et al./France/2001	37.7		10.5		9.9			4.3		6.8	
Mercanti et al./Italy/2001	33.0	0.0	3.5		15.5					6.0	
Jakob et al./Germany/2009	32.0		11.0							8.0	
Llorenç et al./Spain/2015	7.0	0.8	13.0	1	11.0		0.6	1.0		6.0	
Grajewski et al./Germany/2015	48.0	0.0	29.0	0	0.0	0.0	0.0	0.0		0.0	3.0
Barisani-Asenbauer et al./Austria/2015	19.6		7.1		15.8			4.3			
Retrospective observational study in Poland, 2005–2015	29.4	23.5	20.6	6	5.9	5.9	2.9	2.9	2.9	0.0	0.0
Mean prevalence in Europe (own data not included)	30.3	0.3	11.0	0.5	15.5		1.2	6.2		5.3	3.0
Mean prevalence in Europe (own data included)	30.2	6.0	11.8	2.3	16.1		1.6	5.8		3.8	1.5

\* Suspected diagnosis. RIS - radiologically isolated syndrome. Empty boxes: data not available.

In many countries, with the improvement of tuberculosis control, the rate of extrapulmonary forms of tuberculosis is increasing, which has not been observed in Poland. Another explanation is that in Western Europe the increase in the incidence of tuberculosis may be associated with growing numbers of migrants, mainly from Africa and Asia, including countries where tuberculosis has appeared fairly recently and there are no vaccination programs in place, making people more susceptible to the infection. Currently, the population of Poland is ethnically uniform and the immigrants come mainly from Ukraine and other countries of the former USSR [39,63,64].

Limited epidemiological data are available in Poland on the prevalence of systemic diseases which can be associated with uveitis [7,8,65–67]. Review of our local patient records between 2005–2015 in Warsaw, Poland, showed an association with systemic diseases in 16.8% of patients with uveitis

patients, which was generally less than in previously published European studies [33,36,42]. Most frequently, our cases of uveitis were associated with sarcoidosis (6.0%) and multiple sclerosis (4.7%) and seldom with some form of arthritis (0.4%). A similar prevalence of uveitis from sarcoidosis was observed in the patient populations from the Netherlands and Belgium, but not in Portugal, Italy, or Spain [22,25–27,30,32,39,42].

Uveitis can be the first symptom of multiple sclerosis (MS) [65–68]. In Poland, the prevalence of MS in the last 60 years has ranged from 37–91 per 100,000 depending on the region of the country [69]. In our retrospective study, uveitis associated with MS was more common than in other European countries, including the Netherlands, France, Germany, the UK, Spain, and Austria [23,33,36,38–41].

Acute Retinal Necrosis **Rheumatoid Arthritis Established Etiology** White Dot Syndrom **Mulitiple Sclerosis** Reiter Syndrom Foxoplasmosis Fuchs uveitis uberculosis Viral infectio enile Idiopat loxocarosis Sarcoidosis Idiopathic Ankylosin spondyliti Boreliosis Autor/ lepatitis HLA-B27 IRVAN Arthriti AAU RIS County/ Year James/UK/1976 10 7 7 7 10 7 Kijlstraet al./The 44 56 7 5 5 18 2 1.8 0.5 1.1 Netherlands/1987 Palmares/ 37 9.1 12.2 8.8 2.2 63 2.2 1.6 6.2 Portugal/1990 Rothova et al./The 9 0.7 12.1 0.9 30 70 10 6 17 8 1.4 Netheerlands/1992 Latanza/Italy/1993 62 38 0.6 1.3 0.3 13.5 1.3 Smit/The 58 10 10.4 0.47 7 7.2 0.5 1 3 0.5 42 6 1.6 Netherlands/1993 Tran/ 28 72 9 6.2 0.2 6.7 15.4 15.4 14 2.5 1.1Switzerland/1994 Päivönsalo-Hietanen/ 12.8 Finland/1994 Pivetti-Pezzi/ 7.9 2 28 72 7 8 12 0.4 2 Italy/1996 Thean/UK/1996 73 132 27 Päivönsalo-Hietanen/ 2 2 2 0.5 3 Finland/1997 Levecq/ 0 30 70 24.4 0.5 3.5 7.5 6 2 Belgium/1999 Bodaghi/ 34 66 11.8 2.7 4.4 4.9 1.7 11.2 1.5 4 0.4 2.7 France/2001 Mercanti/ 44 56 17.7 2.14 0.8 2.4 11.8 1.4 7 1.7 Italy/2001 Biziorek/ 30 70 Poland/2001 Jakob/ 35 65 4.2 6.9 3.8 4.5 7.1 3.1 4.3 6.1 1 1.4 3.3 Germany/2009 Cimino/Italy/2010 26 74 6.9 22.7 9.2 4.4 1.6 5.3 Jones/UK/2015 6.9 5 2 3.7 3.7 11.5 0.86 11.6 4.5 1 Llorenç/Spain/2015 26 74 7 0.1 0.8 5 0.3 0.1 5 5 0.9 7 1 3 13 15 0.6 Grajewski/ 3.5 0 11.3 10.1 1.8 0 1.9 0 41 59 7.1 9.7 1.9 8.6 2 0 0.4 0.2 Germany/2015 Barisani-Asenbauer 39 0.68 2.44 10.3 61 6.6 3.36 5.4 8.6 1.6 0.8 0.3 2.2 1 /Austria/2015 69 4.2 0.8 10.8 9.2 0.4 0.2 0.2 Fanlo/Spain/2017 7.8 3 2 0,4 31

 Table 13. Etiologic distribution of uveitis in the single center retrospective observational study from Poland (2005–2015) and in published studies from Europe (1976–2017 (% of all uveitis cases reported).

 

 Table 13 continued. Etiologic distribution of uveitis in the single center retrospective observational study from Poland (2005–2015) and in published studies from Europe (1976–2017 (% of all uveitis cases reported).

Autor/ County/ Year	ldiopathic	Established Etiology	Toxoplasmosis	Fuchs uveitis	White Dot Syndrome	Toxocarosis	Sarcoidosis	HLA-B27 AAU	<b>Mulitiple Sclerosis</b>	Ankylosing spondylitis	Viral infection	Acute Retinal Necrosis	RIS	Rheumatoid Arthritis	IRVAN	Tuberculosis	Boreliosis	Juvenile Idiopathic Arthritis	Ulcerative colitis	Hepatitis C	Reiter Syndrom
Retrospective observational study in Poland, 2005–2015	23	77	17.9	12.2	10.4	6	6	5.7	4.7	3.6	2.5	2.5	1.8	1.4	1.4	0.7	0.4	0.4	0.4	0.35	0.35
Mean prevalence in Europe (own data not included)	36.6	63.3	9.4	6.1	7.2	0.5	4.65	8.2	1.3	8.7	7.2	1.6		0.7	0.1	2.3	2.1	2.4	0.2		1.4
Mean prevalence in Europe (own data included)	36	64	9.9	6.5	7.7	1.4	4.7	8	1.7	8.2	7	1.7	1.8	0.8	0.75	2.2	1.9	2.1	0.3	0.35	1.3

RIS – radiologically isolated syndrome; IRVAN – idiopathic retinal vasculitis, aneurysms, and neuroretinitis. Empty boxes: data not available.

 Table 14. Uveitis in the single center retrospective observational study from Poland (2005–2015) and in published studies from Europe (1976–2017.

Country	First author	Year of publication	Unclassifiable (%)	Systemic noninfectious (%)	Infectious (%)	Ocular specific (%)
France	Bodaghi	2001	34.0	25.0	30.0	10.0
Germany	Jakob	2009	0.0	43.7	22.4	34.3
Spain	Llorenç	2015	26.0	25.0	29.0	20.0
Germany	Grajewski	2015	41.0	20.0	17.0	23.0
Austria	Barisani- Asenbauer	2015	39.4	19.5	19.0	19.2
Spain	Fanlo	2017	31.2	29.2	20.0	15.0
Poland	Retrospective observational study in Poland, 2005–2015	2005–2015	23.6	16.8	27.9	31.8

Fuchs uveitis, idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN); radiologically isolated syndrome (RIS); HLA-B27 associated acute anterior uveitis (AAU) without systemic disease; and white dot syndrome (WDS) were included in ocular specific group.

This study had several limitations. A retrospective review of clinical data was conducted at a single center, which was dependent on the quality of the information recorded. A small number of patients was included in this observational study, although records covering a period of 10 years were collected. Also, other European studies included secondary data from

multi-ethnic populations and patients under the age of 18 years who could not be statistically evaluated.

# Conclusions

The difficulties facing epidemiologists in studying the patterns of uveitis are well known and have previously been highlighted by Nashtanei et al., who recommended that classification systems for uveitis should be universally adopted and that population-based studies in all countries should be compared to provide more reliable epidemiological data [70]. The findings of this retrospective observational study conducted in our department in Warsaw, Poland between 2005–2015 and comparison with a review of the published literature from other European countries between 1976–2017 support this view, even though the incidence of causes of uveitis in Poland was similar to those in the rest of Europe. It is possible that any differences in the Polish population arise from genetic, socio-economic, and

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health care, including vaccination programs for certain infections. There may also be differences between countries in the ability to recognize and diagnose uveitis, which results from differences in medical education, medical staff experience, the level of health care, and the availability of diagnostic investigations [45–47]. Because identifying the cause of uveitis is required for appropriate treatment, as we have shown, a multidisciplinary approach to the diagnosis and management of patients with uveitis requires collaboration between the ophthalmologist and a team of specialists in other areas of medicine.

#### **Conflict of interest**

None.

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