Uveitis Subtypes in a German Interdisciplinary Uveitis Center — Analysis of 1916 Patients

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ABSTRACT. ***Objective.*** Studies on the epidemiology of uveitis are rare and cohorts are small. We analyzed the frequencies of classified forms of uveitis in all patients at our center.

Methods. We studied 1916 consecutive patients with inflammatory eye disease. Data were analyzed regarding associated systemic disease, infection, ocular syndromes, anatomic localization, age, and sex.

Results. In 59.1% of patients, a classified form of uveitis was observed: associated systemic diseases in 43.7%, the most frequent ones sarcoidosis (17.4%) and ankylosing spondylitis (16.8%); ocular syndromes in 34.3%, the most frequent HLA-B27-positive anterior uveitis (AU; 35.1%) and Fuchs uveitis syndrome (FUS; 34.3%); and infections in 22.4%, the most frequent herpetic infections (46.1%) and toxoplasmosis (31.5%). We found AU in 45.4% of patients (15.4% HLA-B27-positive AU and 11.3% FUS), intermediate uveitis in 22.9% (unclassified 53.7% and multiple sclerosis 10.3%), and posterior uveitis in 13.5% (24.7% toxoplasmosis). Panuveitis was diagnosed in 6.2% of cases (Behçet's disease 12.6%; sarcoidosis 10.9%). The remaining 12.0% of cases showed extrauveal manifestations (scleritis, episcleritis, keratitis, optic neuritis, myositis, and orbital inflammation).

Conclusion. We describe the largest cohort to date of consecutive patients from a specialized uveitis center. The high frequency of classified disease, nearly 60% in our clinic, shows the usefulness of an interdisciplinary approach, oriented on anatomic presentation. (First Release Dec 15 2008; J Rheumatol 2009;36:127–36; doi:10.3899/jrheum.080102)

Key Indexing Terms:
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Uveitis, the term used for intraocular inflammation of the uvea, is responsible for 5%–20% of cases of legal blindness and 10% of severe visual disorders in the developed nations[1-7]. Frequently, the diagnosis of uveitis conceals ocular involvement related to a systemic disease, an infection, or an ocular syndrome. The specific diagnosis of the underlying disease is difficult to determine and requires interdisciplinary cooperation. Often rheumatologists are asked by an ophthalmologist to "investigate" a patient with uveitis for a rheumatic disease, which is a challenge for the rheumatologist, as uveitis is one diagnosis with heterogeneous subsets that correspond to many diseases[8]. Extensive and costly laboratory and imaging diagnostics are often ordered without giving any result. In order to diagnose associated conditions and recognize treatment necessities without squandering healthcare resources, knowledge of the epidemiology of uveitis is essential. However, studies on the epidemiology of uveitis are rare and usually include small cohorts; and the results are controversial, due to differences in numbers of study participants, geography, quality of classification system, and patient selection.

Progress has been made in recognizing, diagnosing, and classifying uveitis and associated systemic disease. Thus, older epidemiologic studies have their limitations. A precise analysis makes possible an effective approach that incorporates likelihoods of associated diagnoses depending on anatomic localization and patient's sex and age group. We describe the biggest cohort of patients with uveitis from one tertiary referral center published to date, and illustrate the usefulness of this diagnostic approach.

MATERIALS AND METHODS

We performed a retrospective analysis of the medical records of all patients who presented to the Interdisciplinary Uveitis Center at the University of Heidelberg between October 2001 and October 2006. Inclusion criteria were a diagnosis of uveitis, or extrauveal disease as defined below.

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Exclusion criteria were masquerade syndromes (ocular irritation after surgery, trauma, retinal detachment, posterior vitreous detachment, vitreous hemorrhage, or malignancies).

Each patient received an ophthalmologic examination, consisting of visual acuity recordings, slit-lamp examination, tonometry, and indirect ophthalmoscopy. Diagnoses and anatomic classification of uveitis were based on SUN workshop and International Uveitis Study Group criteria[9,10].

For diagnosis of associated diseases a detailed medical history and clinical examination by a rheumatologist were undertaken, and basic tests consisting of blood cell count, chemistry, serum fluorescent treponemal antibody absorption detection, serologic tests for Lyme disease, and chest radiographs were performed. Subsequent tests were ordered depending on suspected associations after interdisciplinary discussions of the case, as described[11]. All findings were entered into a customized electronic database (FileMakerPro® 7.0 v2; FileMaker, Inc.)[12]. A final evaluation of each case was done by one ophthalmologist (MDB). If 2 conditions coexisted, the more prominent condition was considered as the main diagnosis, except for a few cases where 2 diagnoses were judged equally likely to be connected with the eye disease.

The term inflammatory eye disease was used for patients with uveitis as well as patients with extrauveal manifestations (scleritis, episcleritis, keratitis, optic neuritis, orbital inflammation, papillitis, neuroretinitis, and myositis). For analysis, we divided these into unclassified or primary versus classified, also called secondary, cases. The term unclassified was used when no associated condition was found despite extensive examination.

Cases of classified disease were divided into 3 groups: systemic disease, ocular syndrome, or infection. Ocular syndromes included a clearly defined uveitis entity without systemic involvement, such as HLA-B27-associated anterior uveitis (AU; typical unilateral AU with sudden onset and duration < 3 months in HLA-B27-positive individuals without joint involvement) or Fuchs uveitis syndrome (FUS; typical low-grade unilateral anterior intermediate uveitis with insidious onset, chronic course, iris transillumination defects or heterochromia, resistant to local or oral prednisone and with later development of cataract and glaucoma). In addition, data were analyzed for anatomic localization, age of onset, and sex. Out of these epidemiologic data we calculated likelihoods for different uveitis-associated diseases that could be helpful to improve the diagnostic process.

RESULTS

Demographic data. The study included 1916 patients (832 male, 1084 female) with inflammatory eye disease (ratio 0.43:0.57 or 0.77:1), of which 80 and 150, respectively, had extrauveal disease. The median age at onset of eye disease was 35 yrs (range 0–90 yrs). The age distribution (Figure 1) shows disease onset less frequently in those of young age and among the elderly. Patients frequenting our Center are from all over Germany, with a focus on the Southwest.

Classified inflammatory eye disease. We found 35.3% of patients had unclassified and 59.1% had classified inflammatory eye disease. In 2.4% of cases, diagnostics were incomplete but classified disease was suspected. A small percentage of patients (3.2%) were lost to followup before all evaluations had taken place (Figure 2A). Patients with uveal inflammation in particular showed classified disease — 62.4% (1052/1686), in contrast to those with extrauveal inflammation, where unclassified disease predominated with 56.5% (130/230).

Classified uveitis could be subdivided as follows: associated systemic diseases in 41.8% (440/1052), ocular syndromes in 36.9% (388/1052), and infection in 22.0% (231/1052). Five patients were diagnosed with 2 systemic diseases that were possibly linked to their eye disease. In 2 patients an infection with 2 different agents was diagnosed and one patient had 2 ocular syndromes. Another 5 patients were diagnosed with 2 diagnoses out of different groups, e.g., a systemic disease and an infection.

Uveitis and associated systemic disease, ocular syndromes, and infectious conditions. The most frequent forms of classified uveitis in our clinic are shown in Table 1 and Figure 2B. Among the 440 cases of uveitis with associated systemic disease, sarcoidosis (82/440, 18.6%) and ankylosing spondylitis (AS; 83/440, 18.9%) were the most frequent (Table 2).

Of the 388 cases of uveitis with an ocular syndrome, the most frequent ones were HLA-B27-positive AU (136/388, 35.1%) and FUS (133/388, 34.3%; Table 3). FUS is a mild, chronic inflammation restricted solely to the eye, which has a typical clinical presentation often with heterochromia and does not need immunosuppressive therapy.

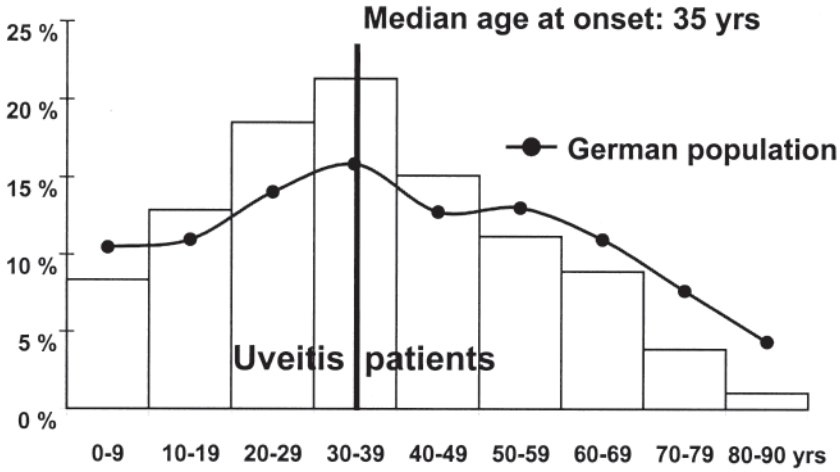

Figure 1. Age distribution at onset of uveitis manifestations in comparison to the German population pyramid (source: Statistisches Bundesamt[47]).

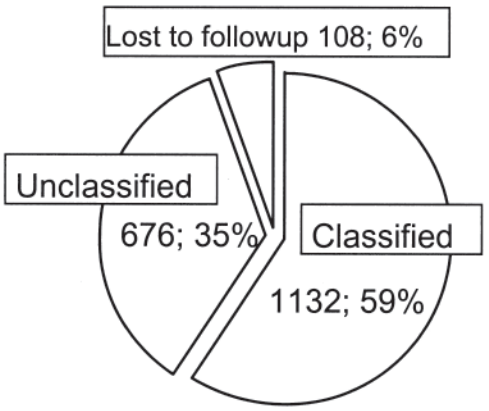

Figure 2A. Ratio of classified and unclassified inflammatory eye disease.

Among the 231 cases of uveitis associated with an infectious condition, the most frequent were herpetic infections (99/231, 42.9%) and toxoplasmosis (80/231, 34.6%; Table 4).

Anatomic localization. AU was found in 45.4% of patients (870/1916), intermediate uveitis in 22.9% (438/1916), and posterior uveitis in 13.5% (259/1916). Panuveitis was found in 6.2% of cases (119/1916; Table 5). The remaining 12.0% of cases were distributed among extrauveal manifestations such as scleritis (107/1916, 5.6%), episcleritis (40/1916, 2.1%), keratitis (33/1916, 1.7%), optic neuritis (18/1916, 0.9%), orbital inflammation (12/1916, 0.6%), papillitis (8/1916, 0.4%), neuroretinitis (8/1916, 0.4%), and myositis (2/1916, 0.1%).

AU was classified in 69.9%, most frequently HLA-B27-

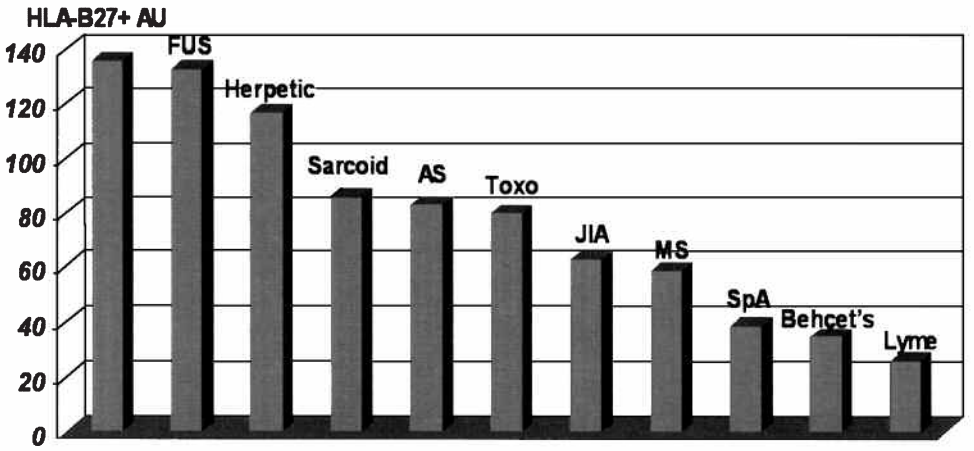

Figure 2B. Most frequent forms of classified uveitis. AU: anterior uveitis; FUS: Fuchs uveitis syndrome; AS: ankylosing spondylitis; Toxo: toxoplasmosis; JIA: juvenile idiopathic arthritis; MS: multiple sclerosis; SpA: spondyloarthropathy.

Table 1. The most frequent associations with inflammatory eye disease in our clinic (percentages do not sum to 100% due to rounding).

Most Common Associations (total n = 1916)	n (%)	Anatomic Location, n					Females, n (%)	Females, adjusted*, %
		Anterior	Intermediate	Posterior	Panuveitis	Extrauveal		
Unclassified	676 (35.3)	215	235	64	32	130	406 (60.1)	46.2
HLA-B27-positive AU	136 (7.1)	136	0	0	0	0	78 (57.4)	44.2
Fuchs uveitis syndrome	133 (6.9)	98	32	0	3	0	45 (33.8)	26.1
Herpetic (VZV, HSV, CMV, EBV, ARN)	117 (6.1)	74	2	15	8	18	68 (58.1)	44.8
Sarcoidosis	86 (4.5)	29	34	6	13	4	47 (54.7)	42.1
AS	83 (4.3)	83	0	0	0	0	25 (30.1)	23.2
Toxoplasmosis	80 (4.2)	0	0	66	14	0	50 (62.5)	48.1
JIA	63 (3.3)	59	2	0	1	1	43 (68.3)	52.6
Multiple sclerosis	59 (3.1)	6	46	1	1	5	44 (74.6)	57.4
Undifferentiated SpA	39 (2.0)	34	2	0	0	3	17 (43.6)	33.6
Behçet's disease	35 (1.8)	4	9	7	15	0	7 (20.0)	15.4
Lyme disease	26 (1.4)	7	6	7	2	4	14 (53.8)	41.5
Incomplete diagnostics	46 (2.4)	18	20	2	2	4	26 (56.5)	43.5
Lost to followup	62 (3.2)	30	10	3	3	16	42 (67.7)	52.2

* Percentages were multiplied by 0.77 for appropriate comparison to account for the male:female ratio. AU: anterior uveitis; VZV: varicella zoster virus; HSV: herpes simplex virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ARN: acute retinal necrosis; AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; SpA: spondyloarthropathy.

Table 2. Associated systemic diseases in patients with inflammatory eye disease (percentages sum to more than 100% due to 5 patients with 2 diagnoses).

Associated Systemic Disease	Uveal Manifestation, n (%) (n = 440)	Extrauveal manifestation, n (%) (n = 55)	Total, n (%) (n = 495)
Sarcoidosis	82 (18.6)	4 (7.3)	86 (17.4)
Ankylosing spondylitis	83 (18.9)	—	83 (16.8)
Juvenile idiopathic arthritis	62 (14.1)	1 (1.8)	63 (12.7)
Multiple sclerosis	54 (12.3)	5 (9.1)	59 (11.9)
Undifferentiated SpA*	36 (8.2)	3 (5.5)	39 (7.9)
Behçet's disease	35 (8.0)	—	35 (7.1)
Rheumatoid arthritis	8 (1.8)	14 (25.5)	22 (4.4)
Ulcerative colitis	16 (3.6)	3 (5.5)	19 (3.8)
Crohn's disease	10 (2.3)	6 (10.9)	16 (3.2)
Psoriasis arthropathy	11 (2.5)	1 (1.8)	12 (2.4)
Reactive arthritis	11 (2.5)	1 (1.8)	12 (2.4)
Tubulointerstitial nephritis and uveitis	10 (2.3)	—	10 (2.0)
Acquired immune deficiency syndrome	8 (1.8)	—	8 (1.6)
Wegener's granulomatosis	3 (0.7)	5 (9.1)	8 (1.6)
Unclassified systemic vasculitis	2 (0.5)	2 (3.6)	4 (0.8)
Vogt-Koyanagi-Harada syndrome	4 (0.9)	—	4 (0.8)
IgA glomerulonephritis	—	3 (5.5)	3 (0.6)
Collagenous diseases	2 (0.5)	1 (1.8)	3 (0.6)
Systemic lupus erythematosus	—	3 (5.5)	3 (0.6)
Churg-Strauss syndrome	—	2 (3.6)	2 (0.4)
Polychondritis	1 (0.2)	1 (1.8)	2 (0.4)
Sacroiliitis	2 (0.5)	—	2 (0.4)
Sjögren's syndrome	1 (0.2)	1 (1.8)	2 (0.4)
Scleroderma	2 (0.5)	—	2 (0.4)
Autoimmune hepatitis	1 (0.2)	—	1 (0.2)

* SpA: spondyloarthropathy.

Table 3. Specific ocular syndromes as a cause of uveitis (percentages sum to more than 100% due to 1 patient with 2 diagnoses).

Uveitis with an Ocular Syndrome, n = 388	Total, n (%)
HLA-B27-positive anterior uveitis*	136 (35.1)
Fuchs uveitis syndrome	133 (34.3)
Ocular sarcoidosis**	22 (5.7)
Multifocal chorioretinitis	15 (3.9)
Birdshot retinochoroidopathy	14 (3.6)
Acute posterior multifocal placoid pigment epitheliopathy	14 (3.6)
Serpiginous chorioretinitis	12 (3.1)
Punctate inner choroidopathy	10 (2.6)
Posner-Schlossman syndrome	10 (2.6)
ANA + chronic anterior uveitis	6 (1.5)
Multiple evanescent white dot syndrome	5 (1.3)
Eales' disease	4 (1.0)
Lens-induced uveitis	3 (0.8)
Acute zonal occult outer retinopathy	2 (0.5)
Acute retinal pigment epitheliitis	2 (0.5)
Acute idiopathic blind spot enlargement syndrome	1 (0.3)

* An ocular syndrome defined as typical unilateral anterior uveitis with sudden onset and < 3 months' duration in HLA-B27+ individuals without systemic manifestation of disease. ** A granulomatous intraocular inflammation compatible with sarcoidosis, combined with elevated levels of angiotensin-converting enzyme but normal chest radiographs.

positive AU, 15.4% (134/870) and FUS, 11.3% (98/870). Counting together all patients with a possible HLA-B27-related disease, including those with AS, inflammatory bowel disease, undifferentiated spondyloarthropathy (SpA), reactive arthritis, HLA-B27-positive AU, and psoriatic arthritis, they sum to 32.2% of cases of AU.

Intermediate uveitis generally was unclassified (235/438, 53.7%). In the classified forms, multiple sclerosis was the most frequent — 10.3% (45/438).

For posterior uveitis, classified forms existed in 71% of patients. Toxoplasmosis was found most often, with 24.7% (64/259).

Panuveitis was classified in 68.9%; Behçet's disease (15/119) and sarcoidosis (13/119) were the most frequent diagnoses (12.6% and 10.9%, respectively).

Uveitis by age distribution and sex. As shown in Figure 1, the very young and the very old were less often affected than the middle aged. The same was true for the classified forms of uveitis; children and the elderly more often showed unclassified uveitis.

For classified uveitis, among the young (≤ 16 yrs), juvenile idiopathic arthritis (JIA) was most frequent, with

Table 4. Infectious conditions as a cause of inflammatory eye disease (percentages sum to more than 100% due to 2 patients with 2 diagnoses).

Infectious Condition	Uveal Manifestation, n (%) (n = 231)	Extrauveal manifestation, n (%) (n = 23)	Total, n (%) (n = 254)
Herpetic infections	99 (42.9)	18 (78.3)	117 (46.1)
HSV	40 (17.3)	12 (52.2)	52 (20.5)
VZV	39 (16.9)	6 (26.1)	45 (17.7)
ARN	10 (4.3)		10 (3.9)
CMV	8 (3.5)		8 (3.1)
EBV	2 (0.9)		2 (0.8)
Toxoplasmosis	80 (34.6)		80 (31.5)
Reactivated	63 (27.3)		63 (24.8)
Scarred	12 (5.2)		12 (4.7)
Freshly infected	5 (2.2)		5 (2.0)
Lyme disease*	22 (9.5)	4 (17.4)	26 (10.2)
Tuberculosis	21 (9.1)		21 (8.3)
Syphilis	4 (1.7)		4 (1.6)
Toxocariasis	4 (1.7)		4 (1.6)
Onchocercosis	2 (0.9)		2 (0.8)
Presumed ocular histoplasmosis syndrome	1 (0.4)		1 (0.4)
Cat scratch disease		1 (4.3)	1 (0.4)

* Lyme disease was diagnosed by positive IgG and confirmed by specific bands in Western blot, but not all patients needed antibiotic treatment. Southern Germany has a high seroprevalence for *Borreliae*, which makes interpretation of serology results difficult. Thus, these results in regard to uveitis must be regarded with caution. VZV: varicella zoster virus; HSV: herpes simplex virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ARN: acute retinal necrosis.

25.3%. Between ages 17 and 29, HLA-B27-positive AU and FUS were most frequent (12.4% and 9.7%). Among middle aged patients (30–65 yrs), a variety of syndromes were found in comparable frequencies: HLA-B27-positive AU 7.9%, AS 5.5%, herpetic infection 5.3%, sarcoidosis 4.4%, FUS 4.9%, and multiple sclerosis 3.3%. In patients older than 65 years, however, uveitis associated with a herpes infection predominated (15.1%). In regard to the herpetic infections, it is necessary to know that often the diagnoses were made clinically and not always verified by polymerase chain reaction testing of aqueous fluid. Most herpetic infections were caused by herpes simplex virus (n = 52), followed by varicella zoster virus (n = 45), cytomegalovirus (n = 8), and Epstein-Barr virus (n = 2).

The male:female ratio of 0.43:0.57 in the whole cohort was similar in the group with classified uveitis (0.47:0.53). Still, several gender preferences could be seen in the subsets of uveitis, even after correction for sex distribution in the cohort (Table 1). Behçet's disease had a strong tendency toward male carriers (84.6%), as did FUS (73.9%) and AS (76.8%), and less so in HLA-B27-positive AU (55.8%). Multiple sclerosis, however, was more frequent in women (57.4%). Birdshot choroidopathy was clearly more frequent in female patients (71.5%). JIA was diagnosed slightly more often in girls, with 52.6%.

Calculation of associated diseases subject to different uveitis patterns. To show the importance of knowledge of epidemiologic data, we calculated disease likelihoods for the most important systemic associations and infections. Different uveitis patterns such as those for anatomic localization, laterality, age, and sex were attributed to the different diseases. AU, for example, was found to be the strongest risk factor for AS. Any patient at our uveitis center with AU has a risk of 9.5% for AS. Taking into consideration more pattern information such as alternating laterality, male sex, and adult age, this likelihood increases to 40.1%. But AU is also a high risk factor for herpetic infection. Here the influence of the additional factors unilateral appearance of inflammation and age increase the likelihood to 38.5%. For toxoplasmosis, posterior uveitis was the strongest risk factor (25.5% for any patient presenting with posterior uveitis). If unilaterality and young age occur as well, the likelihood rises to 68.8%. Further likelihoods for other pattern combinations are presented in Table 6.

DISCUSSION

Classified and unclassified uveitis. We found a frequency of 59.1% for classified inflammatory eye disease in our cohort. Only 35.3% of our patients had unclassified disease as defined above. This corresponds well to the literature for Western Europe and the USA[13-19]. Bodaghi, *et al*[20] found 34% of unclassified disease in France, Tran, *et al*[18] 28% in Switzerland, Thean, *et al*[17] 27% in Great Britain, and Rodriguez, *et al*[15] 34.9% in the US. Banares, *et al*[21] found an even higher rate of 66.8% classified uveitis in Spain. Some older reports or reports from less developed countries gave higher rates of unclassified disease. Palmares, *et al*[22] described 48.5% in Portugal, and Biswas, *et al*[23] found 59.3% and Singh, *et al*[24] 51.2% in India. These numbers might include undiagnosed conditions, due to fewer avail-

Table 5. Anatomic localization of uveitis and most frequent associated causes of uveitis (n ≥ 5).

Anterior 870/1916 (45.4%)	Systemic disease 269/870	Ankylosing spondylitis	83/269
		Juvenile idiopathic arthritis	59/269
		Undifferentiated SpA	34/269
		Sarcoidosis	29/269
		Ulcerative colitis	10/269
		Reactive arthritis	10/269
		TINU	9/269
		Crohn's Disease	7/269
		Multiple sclerosis	6/269
		Psoriasis arthropathy	5/269
	Ocular syndrome 257/870	HLA-B27+ anterior uveitis	134/257
		Fuchs uveitis syndrome	98/257
		Posner-Schlossman	9/257
		Ocular sarcoidosis	7/257
		ANA+ chronic anterior uveitis	6/257
	Infection 82/870	Herpes	74/82
		Lyme disease	7/82
Intermediate 438/1916 (22.9%)	Systemic disease 108/438	Multiple sclerosis	45/108
		Sarcoidosis	34/108
		Behçet's disease	9/108
	Ocular syndrome 51/438	Fuchs uveitis syndrome	32/51
		Ocular sarcoidosis	9/51
	Infection 15/438	Lyme disease	6/15
Posterior 259/1916 (13.5%)	Systemic disease 15/259	Behçet's disease	7/15
		Sarcoidosis	6/15
		AIDS	6/15
	Ocular syndrome 64/259	APMPPE	13/64
		Serpiginous chorioretinitis	12/64
		Birdshot retinochoroidopathy	10/64
		MCP	9/64
		PIC	7/64
		MEWDS	5/64
	Infection 105/259	Toxoplasmosis	64/105
		Tuberculosis	10/105
		Herpes	15/105
		Lyme disease	7/105
Panuveitis 119/1916 (6.2%)	Systemic disease 37/119	Behçet's disease	15/37
		Sarcoidosis	13/37
		Vogt-Koyanagi-Harada disease	3/37
	Ocular syndrome 16/119	Ocular sarcoidosis	5/16
		MCP	5/16
	Infection 29/119	Toxoplasmosis	14/29
		Herpes	8/29
		Tuberculosis	5/29

SpA: spondylarthropathy; TINU: tubulointerstitial nephritis and uveitis, ANA: antinuclear antibody, APMPPE: acute posterior multifocal pigment epitheliopathy, MCP: multifocal choroiditis and panuveitis, PIC: puntate inner choroidopathy, MEWDS: multiple evanescent white dot sydnrome.

able diagnostic means. An argument supporting this is an observed decrease in cases of unclassified uveitis in Japan over the years[25].

Uveitis and associated systemic disease, specific ocular syndromes, and infectious conditions. Among classified uveitis cases, systemic disease was the most frequent association (25.8%). The literature reports rates that are somewhat lower[23,26-29]. Such a high rate of systemic associations in our study we believe is due to the interdisciplinary approach of our center, because particular competent knowledge of different disciplines and mutual discussion of findings are helpful in diagnoses of associated diseases.

Specific ocular syndromes affected fewer patients (20.3%), and this was reflected in the literature[16,25,30]. The most frequent conditions overall, however, clearly belonged to the category of ocular syndromes. These were FUS and HLA-B27-positive AU.

Although the smallest group among the classified forms is represented by infectious conditions (13.3%), their diagnostics are especially important because they require completely different therapies. In our cohort, infections were less frequent than in results found by others[29-31]. The literature agreed with our results in that infection most frequently comprised herpetic infections and toxoplasmosis[20,27,32], 2

diseases that can be detected by the ophthalmologist in most cases on the basis of their clinical picture. This does not apply for the next 2 most frequent infections in uveitis patients, Lyme disease and borreliosis, both diseases that require multidisciplinary management.

Among our cases of classified uveitis, the most frequent were HLA-B27-positive AU, FUS, herpetic infection, sarcoidosis, AS, toxoplasmosis, multiple sclerosis, JIA, SpA, Behçet's disease, and Lyme disease (Table 1, Figure 2B). These frequencies compared well with those in the literature (see Tran *et al*[18] for a review).

Thean, *et al*[17] found frequencies in Great Britain that were similar to ours. Most often, and more so than in most studies including ours, they found HLA-B27-positive AU (15.2%) and FUS (13.2%). Herpes simplex (5.0%), sarcoidosis (4.9%), toxoplasmosis retinitis (4.6%), Behçet's disease (2.4%), and herpes zoster (2.3%) were comparable in frequency.

Tran, *et al*[18] also report HLA-B27-positive AU to be the most frequent, followed by a high rate of herpes zoster (9%) and toxoplasmosis (9%).

Bodaghi, *et al*[20] did not report FUS, herpetic infection, or toxoplasmosis among their most common causes, but instead listed diagnoses such as Vogt-Koyanagi-Harada syndrome (2%). These are rarely seen in Germany — in our cohort only 0.2% had this disease. Behçet's disease too was more frequent in their cohort, with 6.1%. Still, they preselected especially severe, chronic forms of uveitis.

Lyme disease did not seem to be as prominent in other studies as in our patient group; this is due to Lyme disease being endemic in Southern Germany, in an environment of high public awareness. It is common that general practitioners initiate laboratory testing for Lyme disease. There is controversy about the interpretation of serology results. We require positive IgG findings and specific bands in Western blot tests for a diagnosis, but this approach has its limits.

The differences in causes of uveitis reflect regional and genetic factors. For instance, Behçet's disease is rare in the USA and Europe, while it is frequent in countries along the ancient Silk Road. Dutch authors report 1.7% of Behçet's disease among uveitis patients[16]; in contrast, from Taiwan a much higher 17.9% is reported[33].

HLA-B27-associated diseases, in contrast, are more common among Caucasians[34]. HLA-B27-positive AU is more frequent in Northern Europe[35] than in California[14] or Italy[31]. Surprisingly, there was also a high count of HLA-B27-positive AU in Taiwan[33].

Uveitis and anatomic localization. Anatomic localization can give useful information to the clinician about the likely cause of uveitis[21]. As in our cohort, with 45.4%, AU is described in the literature as the most common form of uveitis[15,16,18,21,26,28,35]. In general practice it is even more frequent[18]. The most frequent forms of AU in our collective and in the literature are HLA-B27-positive AU and FUS. If the AU is not explained by an ocular syndrome alone, our data indicate consideration of AS or undifferentiated SpA. Sarcoidosis also appears often as AU, but just as often in an intermediate form.

For intermediate uveitis, our results agree with the literature in that classified forms are rare[15,20,36-38]. If they occur, they represent systemic disease, often multiple sclerosis. Intermediate uveitis is rare in an office of general ophthalmology (1% versus 12% in a tertiary care center)[26]. We found an even higher percentage, with 22.9%.

Posterior uveitis existed in 13.5% of our patients, and as reported is most commonly caused by toxoplasmosis[13,15,27,30,39,40]. It is found more frequently in tertiary care centers than in general practice (15% versus 5%)[26]; the same is true for panuveitis (9% versus 1%). Panuveitis is also the rarest uveitis presentation, 6.2% in our cohort.

In both posterior uveitis and panuveitis associated systemic diseases are rare; sarcoidosis should be considered in both cases. Further, in the case of a posterior inflammation, Behçet's disease should be excluded, especially if the patient comes from a Mediterranean, Arab, or Asian area.

If extrauveal inflammation such as scleritis occurs, the strategy in the search for the associated disease should focus on rheumatoid arthritis (RA), and if there are other corresponding indications on inflammatory bowel diseases.

Uveitis and age and sex distribution. The age distribution in our study population seems representative. Other authors found similar mean ages at uveitis onset of 33 years[30], 34 years[32],37 years[15], and 44 years[29]. Our observation that uveitis is less common among the young and the elderly is supported by the literature[21,30,41].

Differences in distribution of uveitis between age groups were found. For children with AU, for example, JIA is a frequent diagnosis[42-46].

The literature offers some dissent about the male to female ratio in uveitis. Some studies report that more men present with uveitis[17,23,24,27]; some report more women[21,25,30,41] (range 1.6:1 to 0.7:1, respectively). With 0.77:1 (or 0.43:0.57), our collective showed a female-oriented ratio. This rate differs from the sex distribution in the general population in Germany, where until age 50 years, men are slightly more numerous (0.51:0.49)[47]. The specific patterns of distribution in subsets of uveitis by sex are presented in Table 1.

With Table 6 we present an analysis of disease likelihoods depending on various uveitis patterns. These data offer guidance from the ophthalmologic presentation toward a rheumatologic diagnosis and help to facilitate efficient diagnostic testing. In a best-case scenario the ophthalmologic picture can be communicated by the ophthalmologist to the rheumatologist and with the help of these likelihood data, specific testing can take place.

As our study contains such a large number of patients, we were able to calculate the risk of the most important systemic diseases and infections for different pattern combina-

Table 6. Schematic for diagnosis of the most common systemic associations and underlying infections of uveitis (ocular syndromes are not included because they are diagnosed by the ophthalmologist based on morphologic appearance only). Likelihood of disease: prevalence of disease in the current groups based on pattern considered.

1st Pattern: Localization of Inflammation	Most Frequent Diagnosis	Likelihood, %	2nd Pattern: Laterality	Likelihood, %	More Patterns (characteristic risk factors): Age, Sex	Likelihood, %
Anterior	Ankylosing spondylitis	9.5	Alternating	27.7	Anterior, alternating, adult male patient	40.1
			Unilateral	9.0		
			Bilateral	6.6		
	Herpes	8.5	Unilateral	12.4	Anterior, unilateral, patient > 65 yrs old	38.5
			Bilateral	2.1		
	Juvenile idiopathic arthritis	6.8	Bilateral	11.8	Anterior, bilateral, patient < 16 yrs old	42.6
			Unilateral	4.3	Anterior, unilateral, patient < 16 yrs old	35.7
	Undifferentiated SpA	3.9	Unilateral	3.9		
			Bilateral	3.8		
	Sarcoidosis	3.3	Bilateral	5.2	Anterior, bilateral, female patient > 65 yrs	7.1
			Unilateral	2.2		
	Inflammatory bowel disease	2.0	Bilateral	3.5	To take more patterns into consideration does not increase the likelihood of disease	
			Unilateral	1.2		
Intermediate	Multiple sclerosis	10.5	Bilateral	11.2	Intermediate, bilateral, female	13.1
			Unilateral	8.2		
	Sarcoidosis	7.8	Bilateral	8.6	Intermediate, bilateral, patient > 65 yrs old	11.1
			Unilateral	4.1		
	Behçet's disease	2.1	Bilateral	2.2	Risk factor was patient from the "silk road," but data on race were not noted in patient's records	
			Unilateral	1.6		
	Lyme disease	1.4	Bilateral	1.6	To take more patterns into consideration does not increase the likelihood of disease	
			Unilateral	0.8		
Posterior	Toxoplasmosis	25.5	Unilateral	41	Posterior, unilateral, patient < 16 yrs old	68.8
			Bilateral	9.7		
	Herpes	5.8	Bilateral	6.0	Further patterns must be found specifically, since most of the posterior uveitis forms are infectious	
			Unilateral	5.7		
	Tuberculosis	3.9	Bilateral	5.2		
			Unilateral	1.6		
	Lyme disease	2.7	Bilateral	3.7		
			Unilateral	1.6		
	Behçet's disease	2.7	Bilateral	3.0		
			Unilateral	2.5		
	Sarcoidosis	2.3	Bilateral	3.0		
			Unilateral	1.6		
Panuveitis	Behçet's disease	12.6	Bilateral	15.9	Since panuveitis is the rarest form of uveitis, even with our large cohort we were not able to determine likelihoods with further patterns, especially as we do not have data on race of patients originating from the "silk road"	
			Unilateral	5.6		
	Toxoplasmosis	11.8	Bilateral	30.6		
			Unilateral	3.7		
	Sarcoidosis	10.9	Bilateral	15.9		
			Unilateral	We saw no patient with this combination		
	Herpes	6.7	Unilateral	22.2		
			Bilateral	We saw no patient with this combination		
	Tuberculosis	4.2	Unilateral	8.3		
			Bilateral	2.4		
Extrauveal	Herpes	7.8	Unilateral	10.7	Unilateral, extrauveal, patient > 65 yrs old	18.2
			Bilateral	2.5		
	Rheumatoid arthritis	6.1	Bilateral	7.4	Bilateral, extrauveal, patient > 65 yrs old	27.3
			Unilateral	5.4		
	Crohn's disease	2.6	Bilateral	4.9	To take more patterns into consideration does not increase the likelihood of disease	
			Unilateral	2.0		
	Multiple sclerosis	2.2	Bilateral	2.5	To take more patterns into consideration does not increase the likelihood of disease	
			Unilateral	2.0		

tions on the basis of their prevalences in the different subgroups. It should not go unnoticed that these calculations are based on our specific data and patient cohort. Although the authors consider that these calculations can also be useful in other centers, because as mentioned above, other authors reported similar distributions for most of the underlying diseases. Transmitting our calculations to another center it is naturally necessary to regard the regional and genetic differences in the patient cohort.

Banares, *et al*[21] also calculated disease likelihoods based on uveitis patterns in 407 patients; their calculations for AU are very similar to our results. With our larger study, we can confirm their results for AU. The most likely systemic association for a patient with AU is any form of SpA. Taking into consideration other patterns such as laterality (alternating), sex (male), and age (adult patient) can increase the likelihood up to 40.1%. The most common infection associated with AU is herpetic infection. Risk-increasing factors are higher age, unilaterality, and the presence of keratouveitis.

In our study, intermediate uveitis was the strongest risk factor for multiple sclerosis, especially in women with bilateral disease, which confers a disease risk of > 13%. This differs from Banares, *et al*, where only one case of multiple sclerosis is reported; this is due to multiple sclerosis being very rare in Spain[21]. In their report, sarcoidosis was the most probable underlying disease but Behçet's disease and Lyme disease are also noted. In our study, intermediate uveitis was also a high risk factor for sarcoidois; however, sarcoidosis can occur with various patterns of uveitis and thus should be excluded in every uveitis patient at least by chest radiograph, especially in those with bilateral involvement where the risk is generally higher for sarcoidosis.

Posterior uveitis is generally a risk factor for an infectious disease, most commonly toxoplasmosis. Further risk for toxoplasmosis is in unilateral involvement at young age; in this case the calculated disease probability amounts to 68.8%. Banares, *et al*[21] reported that unilateral chorioretinitis was associated almost exclusively with toxoplasmosis in their study. But as shown in Table 6, other infections like herpes, tuberculosis, and Lyme disease should be taken into consideration for patients with posterior uveitis.

A patient with panuveitis has a high risk for Behçet's disease (12.6%), especially if a genetic predisposition is present. This compares closely to the observations of Banares, *et al*[21].

In patients with extrauveal inflammation the authors recommend excluding RA, especially in elderly patients with bilateral inflammation, because nearly every third of this risk group is affected by RA.

We hope that our diagnostic approach following anatomic localization of uveitis and the epidemiologic data given here may recommend specific diagnostic steps in a given patient with uveitis. For the rheumatologist, knowledge of the distribution of different patterns of uveitis is of great value because at least a quarter of all forms of uveitis are associated with a systemic disease that is often hard to detect. The high frequency of 59.1% of classified uveitis in our cohort reflects the value of this approach.

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