


Uveitis causes according to immune status of patients

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ABSTRACT.

Purpose: The advances in medicine have led to an increased number of people living with some form of immunodeficiency. Most ocular infections in immunocompromised patients may lead to irreversible blindness. We identify the causes of uveitis in immunocompetent and immunocompromised patients.

Methods: A retrospective cohort study of 1354 consecutive patients. All patients underwent a standard work-up for uveitis.

Results: An immunocompromised state was identified in 171/1354 patients (13%), of whom 40 had Human immunodeficiency virus (HIV) infection, 52 received immunosuppressive medications, 28 had concurrent malignant disorder and 20 had other causes for their immunosuppression. In addition, 93/1354 patients (7%) had diabetes mellitus (DM). The prevalence of intraocular infections was much higher in immunocompromised patients than in immunocompetent patients and DM ($p < 0.001$). Causes of uveitis differed between the diverse immunocompromised groups. The non-HIV immunocompromised patients showed primarily intraocular herpes simplex and varicella zoster virus infections, whilst HIV-positive patients exhibited frequently cytomegalovirus (CMV) retinitis and syphilis. Patients with generalized malignancies were characterized by a lower prevalence of infections and higher prevalence of sarcoidosis. Patients with DM typically showed sarcoidosis and bacterial intraocular infections. The percentage of undetermined uveitis diagnoses was markedly lower in immunosuppressed patients ($p < 0.001$).

Conclusion: In immunocompromised patients with uveitis, infections were diagnosed in 46% of cases in contrast to 12% in the immunocompetent patients. The causes of uveitis differed among the various types of immunosuppression. Immunocompromised patients with uveitis require a rapid assessment for the most expected infections.

Key words: diabetes mellitus – immunosuppression – infections – malignancy – transplantations – uveitis

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Introduction

Uveitis is a clinical syndrome of multiple origins, which can lead to permanent visual impairment and blindness. Uveitis can be principally divided into infectious or non-infectious category and the early distinction is essential for the treatment and visual outcome of the patients.

The advances in therapy for malignancies and autoimmune disorders together with the improved options in transplantation medicine have led to an increased number of people living with some form of immunodeficiency. Obviously, the specific causes and clinical impact of uveitis differ between immunocompromised and immunocompetent patients. In immunocompetent patients, the most frequently encountered uveitis types are associated with systemic non-infectious immune mediated diseases (Barisani-Asenbauer et al. 2012; Bajwa et al. 2015; Jones 2015; Llorenç et al. 2015; Luca et al. 2017; Zagora et al. 2017). In contrast, the causes of uveitis in immunocompromised patients include predominantly opportunistic infections (Westeneng et al. 2007). Recognition of the exact cause of uveitis in immunocompromised patients is challenging, as clinical features are commonly overlapping, infections might have multiple origins and moreover, results of laboratory tests are often not reliable. Moreover, since serologic tests are not informative on local processes occurring in the eye, the confirmation of infection from intraocular fluid samples is imperative.

Herein, we assess the immune status of 1354 consecutive patients with uveitis and relate the causes of intraocular inflammation to the immune status of the patients.

Patients and Methods

Study population

We conducted a retrospective cohort study at the department of Ophthalmology of the Erasmus Medical Center (Rotterdam, The Netherlands), which represents a tertiary referral centre. This study was performed with the approval of the Medical Ethics Committee of our institution. All data were extracted from medical records of patients and the research has followed the Tenets of the Declaration of Helsinki.

Between September 2012 and December 2016, 1454 consecutive patients with uveitis were seen in our institution. Excluded were 23 patients, of whom clinical data from the time of onset of uveitis were lacking. An additional 77 patients with masquerade syndromes were excluded, including 22 with malignant disease (16 with large B-cell lymphomas, 2 with iris metastases of a carcinoma, 1 with retinoblastoma, 1 with a melanoma, 1 with a medulloepithelioma and 1 patient with chronic lymphatic leukaemia) and 55 with benign masquerade syndromes (19 with hereditary ocular disorder, 17 with vascular, 6 with degenerative and 3 with neurological diseases, 3 with retinal detachments, 4 with chronic serous chorioretinopathy, and 2 with complications following intraocular surgery). Finally, we included 1354 patients with uveitis in the present study.

All patients underwent a standard work-up for uveitis, which included erythrocyte sedimentation rate, blood counts, serum angiotensin-converting enzyme levels, serology for syphilis as well as interferon gamma release assay test (QuantiFERON-TB Gold In-Tube test). Radiologic chest imaging was also performed. Human Leukocyte Antigen B27 testing was performed in patients with anterior and panuveitis. According to the clinical manifestations, additional examinations and referral to appropriate specialists were performed (tailored approach). The addition of the QuantiFERON-TB Gold In-Tube test to the screening was performed in 2013. Human immunodeficiency virus (HIV)

test was not included in a routine work-up for uveitis and was included in all patients with positive syphilis serology and in patients in whom HIV infection was suspected because of clinical presentation and/or medical history. Definitive anatomical classification was performed (e.g. localization and laterality of uveitis) according to the Standardization of Uveitis Nomenclature (SUN) Working Group (Jabs et al. 2005).

Diagnoses were grouped into infectious and non-infectious diseases and in established clinical ocular syndromes (e.g. birdshot chorioretinopathy). Patients with established ocular syndromes and identified cause or association with systemic disorder (e.g. Fuchs uveitis syndrome with documented rubella virus infection or pars planitis with multiple sclerosis) were classified according to the cause of their uveitis and not according to their ocular syndrome (Jabs et al. 2005). Patients with a positive Interferon Gamma Release Assay test in the presence of unexplained uveitis were classified as of unknown origin. All intraocular infections were proven by intraocular fluid analysis with some exceptions: ocular syphilis was diagnosed in patients with positive serologic reactions indicating active syphilis. Ocular tuberculosis was diagnosed only in patients with uveitis and active systemic tuberculosis infection proven either by culture or PCR from affected organs. The diagnosis of definitive sarcoidosis was based on histological confirmation and the diagnosis of presumed sarcoidosis on radiologic abnormalities consistent with the

diagnosis of sarcoidosis (mostly symmetrical hilar lymphadenopathy) (Herbert et al. 2009). Patients with laboratory features suggesting sarcoidosis but without tissue biopsy or typical radiologic features were diagnosed as of unknown origin (Acharya et al. 2018). Histological features of sarcoid reactions in malignancy cannot be histologically differentiated from genuine sarcoidosis as the main difference lies in location of the lesions and concurrent malignancy (Tchernev et al. 2014). Since patients with ocular sarcoidosis might have extrapulmonary involvement only, all patients with positive tissue biopsies were classified as sarcoidosis and subsequently, patients with malignancy and sarcoid reactions are indicated separately. Human leukocyte antigen (HLA) B27-associated uveitis was classified as a systemic immune mediated disorder (whether or not with proven ankylosing spondylitis). Our policy is to refer to rheumatologist (or other specialist) solely HLA B27-positive patients with rheumatologic complaints. In consequence, not all patients underwent rheumatologic evaluation and the exact prevalence of HLA B27-associated systemic disease is not known. As we believe that HLA B27-associated uveitis is the same entity whether or not associated with ankylosing spondylitis, we decided to categorize the patients in the same group. All other specific diagnoses were performed according to current diagnostic criteria. None of our patients used immune checkpoint inhibitors or other immunostimulatory drugs.

Table 1. Criteria for Immune Deficiency or Suppression (adapted from Bonten et al. 2015).

Presence of 1 or more of the following conditions:

Congenital immunodeficiency syndromes
Human immunodeficiency virus (HIV) infection and CD4+ cells <300/mm ³
Sepsis and short recovery period immediately after major surgery
Leukemia (presence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years)
Lymphoma (presence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years)
Hodgkin disease (presence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years)
Multiple myeloma (presence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years)
Generalized malignancy (defined as presence of any malignancy that had been treated by or had been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years)
Receipt of an organ or bone marrow transplant
Concurrent use of immunosuppressive therapy, including steroids in the daily dose above 7.5 mg for at least 4 weeks. (Inhaled, intraarticular and topical steroids were not considered immunosuppressive.)
Chronic renal failure (defined as receipt of renal dialysis or transplant) or nephrotic syndrome

Criteria for an immunocompromised state were based on the earlier definition of Bonten et al. (2015) with some modifications (Table 1). Immunosuppressed patients were further subdivided according to their HIV status, the reasons for immunosuppressive therapy (transplantations, malignancy and non-malignant disease), and other causes of their immune impairment.

Diabetes mellitus (DM) is associated with impaired innate and adapted immune responses and is characterized by an increased risk of infections and their complications (Berrou et al. 2013; Hodgson et al. 2015; Jafar et al. 2016). Hyperglycaemia, impaired neutrophil migration and phagocytosis as well as the state of chronic inflammation in DM are herein involved. Immune responses during pregnancy are shifted towards an anti-inflammatory status, which is advantageous for the outcome of pregnancy but might influence the course of immune-mediated disorders and infections (Robinson & Klein 2012; Graham et al. 2017). Though not immunosuppressed, pregnant females might show a different spectrum of uveitis and therefore are specified separately as well as patients with DM and HIV infections and CD4+ T cell counts above 300 cells/mm³. The following characteristics were extracted: gender, race, age at onset of uveitis, established causes of uveitis and/or associated systemic diseases.

Results

The anatomical classification of uveitis is depicted in Table 2. Immune status of the patients and classification of

uveitis are presented in Table 3. Immune deficiency or suppression was identified in 171/1354, 13% of all patients. The prevalence of posterior uveitis was higher in immunocompromised patients (79/171 versus 258/1075; $p < 0.001$).

The prevalence of infections was much higher in immunocompromised patients compared to immunocompetent patients (78/171, 46% versus 125/1075, 12%; $p < 0.001$). The most prevalent infections in immunocompromised patients were viral infections, particularly cytomegalovirus (CMV), followed by herpes simplex virus (HSV) and varicella zoster virus (VZV). Viruses represented most common infections also in immunocompetent patients, but included predominantly infections with rubella virus and HSV/VZV. All immunocompetent patients with CMV ($n = 3$) had anterior uveitis. The percentage of undetermined uveitis diagnoses was similar in immunocompetent patients and patients with DM, but was lower in immunosuppressed patients (35/171 versus 420/1075, $p < 0.001$).

Diabetes mellitus (DM) at onset of uveitis was present in 93/1354, 7% patients. Patients with DM had a low prevalence of infectious uveitis, similar to immunocompetent patients (8/93, 9% versus 125/1075, 12%; $p = 0.378$). Patients with DM typically suffered from bacterial intraocular infections (mostly endogenous endophthalmitis, Table 3).

The number of pregnant patients and HIV-positive patients with CD4 cells above 300/mm³ was limited and did not allow meaningful comparisons. Majority of HIV-positive patients with CD4+ T cells above 300/mm³ had infectious uveitis, mostly syphilis.

Various types of immune impairment and causes of uveitis are depicted in Table 4. Out of 171 immunocompromised patients, 40 had HIV infection with CD4 positive cells < 300 cells/mm³ and 52 received immunosuppressive medications (17 for organ and/or stem cell transplants, 18 for malignant disorders and 17 for not malignant diseases). No differences in uveitis causes or associations were noted when patients with the various causes for immunosuppressive therapy were compared. In the 17 patients who developed uveitis after stem cell/organ transplant, the interval time between transplant and onset of uveitis was 36 months. Only one transplant patient developed uveitis during his prophylactic regimen with antibiotic and antiviral drugs. Three transplant patients had concurrent systemic infection (2 had candidemia related to their ocular disorder and one had human metapneumovirus infection) and one additional patient had localized VZV in the V1 dermatome. Of the 15 patients with haematological malignancy, 10 had intraocular infections (5 HSV/VZV, 4 CMV, 1 candida). Further, 28 patients had generalized malignancy (but no current immunosuppressive treatment) and 22 had other various causes for their immunosuppression, such as congenital immunodeficiency, sepsis and others. Additional 31 patients received immunosuppressive medications for their systemic disease, which also caused their uveitis (e.g. sarcoidosis, Behcet's disease, inflammatory bowel disease). These patients developed uveitis while on immunosuppressive treatment for systemic disorder and their uveitis improved with the increase of immunosuppressive medication. The development of uveitis in these patients was therefore not related to their immunosuppression.

The spectrum of infections in various immunocompromised groups

HIV-positive patients exhibited most frequently CMV retinitis, followed by syphilitic uveitis whilst the non-HIV immunosuppressed patients had most commonly intraocular HSV/VZV infections. Cytomegalovirus (CMV) infections (all retinitis) developed also in non-HIV patients, specifically in patients with hematologic malignancies ($n = 4$), receiving immunosuppressive therapy for not malignant disease

Table 2. Anatomical classification of uveitis according to immune status of the patients*.

	No evidence of immune suppression (N = 1075) N (%)	Diabetes mellitus [†] (N = 93) N (%)	Immune deficiency or suppression, total [‡] (N = 171) N (%)
Anterior	386 (36)	36 (39)	55 (32)
Intermediate	107 (10)	5 (5)	6 (3)
Posterior	258 (24)	18 (19)	73 (43)
Panuveitis	291 (27)	27 (29)	32 (19)
Scleritis/sclerouveitis	33 (3)	7 (7)	5 (3)

* Not included are 8 patients with HIV infection with CD4+ T cells > 300 cells/mm³ and 7 pregnant patients).

[†] Excludes all with corticosteroid-induced diabetes mellitus.

[‡] Includes 31 patients with not infectious systemic disease, which was also associated with their uveitis. These patients developed uveitis despite their current immunosuppressive treatment and uveitis improved in all with an increase of immunosuppressive therapy.

Table 3. Causes of uveitis according to specific immunocompromised or immunocompetent status of the patients.

	Total (N = 1354) N (%)	No evidence of immune suppression (N = 1075) N (%)	Diabetes mellitus* (N = 93) N (%)	Immune deficiency or suppression, total† (N = 171) N (%)	HIV, CD4 > 300 cells/mm ³ (N = 8) N (%)	Pregnancy (N = 7) N (%)
Infections	220 (16)	125 (12)	8 (9)	78 (46)	7 (87.5)	2 (28)
Viral, total	111 (50)	61 (49)	3 (38)	47 (60)	-	-
Cytomegalovirus	24 (11)	3 (2.5)	-	21 (27)	-	-
HSV/VZV	45 (21)	23 (18.5)	3 (38)	19 (24)	-	-
Rubella	30 (14)	28 (22.5)	-	2 (2.5)	-	-
Others	12 (5.5)	7 (5.5)	-	5 (6.5)	-	-
Bacterial, total	43 (20)	18 (1.6)	4 (50)	14 (18)	6 (86)	1 (50)
Treponema pallidum	12 (5.5)	-	-	7 (9)	-	-
Others	31 (14)	18 (1.6)	4 (50)	7 (9)	5 (71)	1 (50)
Fungi, total	7 (3)	1 (0.08)	-	6 (8)	-	-
Candida	5 (2)	-	-	5 (6)	1 (14)	-
Aspergillus	2 (1)	1 (0.08)	-	1 (1)	-	-
Others	-	-	-	-	-	-
Parasites	58 (26)	45 (4)	1 (13)	11 (14)	-	1 (50)
Toxoplasma gondii	58 (26)	45 (4)	1 (13)	11 (14)	-	1 (50)
Not infectious systemic disease	445 (33)	360 (33)	37 (40)	45 (26)	1 (12.5)	2 (28)
Sarcoidosis	185 (42)	148 (41)	21 (57)	16 (36)	-	-
HLA B27- associated	83 (19)	74 (20.5)	2 (5.5)	4 (9)	1 (100)	2 (100)
Juvenile idiopathic arthritis	48 (11)	44 (12)	-	4 (9)	-	-
Behcet's disease	28 (6)	25 (7)	-	3 (7)	-	-
VKH disease	17 (4)	17 (5)	-	-	-	-
Inflammatory bowel disease	18 (4)	15 (4)	1 (3)	2 (4.5)	-	-
Granulomatous polyangiitis	11 (2)	6 (1.6)	3 (8)	2 (4.5)	-	-
TINU syndrome	7 (1.5)	5 (1.4)	-	2 (4.5)	-	-
Psoriatic arthritis	8 (2)	4 (1)	1 (3)	3 (7)	-	-
SLE	4 (0.9)	-	1 (3)	3 (7)	-	-
Others	36 (8)	22 (6)	8 (22)	6 (13)	-	-
Neurological disease	29 (2)	27 (2.5)	1 (1)	1 (0.5)	-	-
Ocular clinical syndrome	168 (12)	143 (13)	11 (12)	12 (7)	-	2 (28)
Birdshot chorioretinopathy	61 (36)	57 (40)	3 (27)	1 (8)	-	-
White dots syndromes‡	21 (12.5)	19 (13)	-	-	-	2 (100)
Fuchs uveitis syndrome§	14 (8)	12 (8)	2 (18)	-	-	-
Toxic uveitis	9 (5)	3 (2)	2 (18)	4 (33)	-	-
Others	63 (37.5)	52 (36)	4 (36)	7	-	-
Undetermined	492 (36)	420 (39)	36 (39)	35 (20)	-	1 (14)

HIV = human immunodeficiency virus, HLA = human leukocyte antigen, HSV = herpes simplex virus, SLE = systemic lupus erythematoses, TINU = tubulointerstitial nephritis and uveitis, VKH = Vogt-Koyanagi-Harada, VZV = varicella zoster virus.

* Excludes all with corticosteroid-induced diabetes mellitus.

† Includes 31 patients with not infectious systemic disease, which was also associated with their uveitis. These patients developed uveitis despite their current immunosuppressive treatment and uveitis improved in all with an increase in immunosuppressive therapy.

‡ Other cases than birdshot chorioretinopathy.

§ Includes solely cases with unexplained cause and negative and/or not available intraocular fluid analysis.

(*n* = 2), after organ transplant (*n* = 1) and in congenital immunodeficiency syndrome (*n* = 1). Syphilis was an important cause of intraocular infection in HIV-positive population; out of all 48 HIV-positive patients (independently of their CD4 count), 11 (23%) had uveitis due to syphilis. Out of

these, 6/11 (55%) were not aware of their positive HIV status, which became known during the work-up for their uveitis. Fungal infections did not occur in HIV, but were observed in patients on immunosuppressive medications and in patients with other causes of immunosuppression (two

posttransplant patients, one with haematological malignancy during chemotherapy, one during sepsis after major surgery, one with congenital immune deficiency syndrome and one with chronic pancreatitis). Associated systemic non-infectious diseases were scarce in immunosuppressed patients

Table 4. Causes of uveitis in immunocompromised patients.

	Immune deficiency or suppression total N = 171 N (%)	HIV+, CD4 < 300 cells/mm ³ N = 40 N (%)	Immunosuppressive therapy (HIV negative)* N = 52 N (%)	Malignant disease, no immunosuppressive treatment N = 28 N (%)	Remaining causes of immunosuppression N = 20 N (%)	Immunosuppressive therapy for underlying disease which caused uveitis N = 31 N (%)
Infections	78 (46)	28 (70)	29 (56)	7 (25)	14 (70)	0
Viral, total	47 (60)	18 (64)	19 (65.5)	6 (86)	4 (18)	-
Cytomegalovirus	21 (27)	13 (46)	7 (24)	-	1 (4.5)	-
HSV/VZV	19 (24)	1 (3.5)	11 (38)	5 (71)	2 (9)	-
Rubella	2 (2.5)	-	-	1 (14)	1 (4.5)	-
Others	5 (6.5)	4 (14)	1 (3.5)	-	-	-
Bacterial, total	14 (18)	8 (20)	1 (3.5)	-	5 (23)	-
Treponema pallidum	7 (9)	6 (15)	-	-	1 (4.5)	-
Others	7 (9)	2 (7)	1 (3.5)	-	4 (18)	-
Fungi, total	6 (8)	-	3 (10)	-	3 (14)	-
Candida	5 (6)	-	3 (10)	-	2 (9)	-
Aspergillus	1 (1)	-	-	-	1 (4.5)	-
Others	-	-	-	-	-	-
Parasites	11 (14)	2 (7)	6 (21)	1 (14)	2 (9)	-
Toxoplasma gondii	11 (14)	2 (7)	6 (21)	1 (14)	2 (9)	-
NISD, total	45 (26)	2 (5)	4 (8)	6 (21)	2 (10)	31
Sarcoidosis	16 (36)	2 (100)	1 (25)	5 (83)	-	8 (26)
HLA B27-associated	4 (9)	-	1 (25)	1 (17)	-	2 (6)
Juvenile idiopathic arthritis	4 (9)	-	-	-	-	4 (13)
Behcet's disease	3 (7)	-	-	-	-	3 (10)
VKH disease	-	-	-	-	-	-
Inflammatory bowel disease	2 (4.5)	-	-	-	-	2 (6)
Granulomatous polyangiitis	2 (4.5)	-	-	-	-	2 (6)
TINU syndrome	2 (4.5)	-	-	-	-	2 (6)
Psoriatic arthritis	3 (7)	-	-	-	-	3 (10)
SLE	3 (7)	-	-	-	1 (50)	2 (6)
Others	6 (13)	-	2 (50)	-	1 (50)	3 (10)
Neurological disease	1	-	-	1	-	-
Ocular clinical syndrome, total	12 (7)	2 (5)	4 (8)	6 (21)	-	-
Birdshot chorioretinopathy	1 (8)	-	-	1 (17)	-	-
White dots syndromes*	-	-	-	-	-	-
Fuchs uveitis†	-	-	-	2 (33)	-	-
Toxic uveitis	4 (33)	-	2 (50)	3 (50)	-	-
Others	7	2 (100)	2 (50)	-	-	-
Undetermined	35 (20)	8 (20)	15 (29)	8	4 (20)	-

HIV = human immunodeficiency virus, HLA = human leukocyte antigen, HSV = herpes simplex virus, SLE = systemic lupus erythematoses, TINU = tubulointerstitial nephritis and uveitis, VKH = Vogt-Koyanagi-Harada, VZV = varicella zoster virus.

* Other cases than birdshot chorioretinopathy.

† Includes solely cases with unexplained cause and negative and/or not available intraocular fluid analysis.

with uveitis, with the exception of 5 biopsy-proven sarcoid reactions in patients with malignancies (2 with non-Hodgkin lymphoma, 1 with Hodgkin's disease, 1 with non-seminoma testis and 1 with combination of rectum and lung carcinoma). Uveitis in

these patients was consistent with the diagnosis of ocular sarcoidosis and exhibited mostly features of multifocal chorioretinitis. The assessment of intraocular fluid samples in these 5 patients was negative for malignant cells.

Non-infectious uveitis entities

The prevalence of systemic immune-mediated diseases did not differ across the groups with sarcoidosis being the most prevalent in all groups (immuno-competent, immunocompromised and

DM patients). Established ocular entities were less prevalent in immunocompromised patients 12/171; 7% versus 143/1075; 13%. $p = 0.021$). The major causes consisted of birdshot chorioretinopathy in immunocompetent patients and toxic reactions to medications (cytarabine) in the immunosuppressed group.

Discussion

Our study shows a prevalence of 13% of immunocompromised patients in the uveitis population from a tertiary referral centre. We confirm the previously acknowledged high prevalence of infectious uveitis in immunocompromised patients (Westeneng et al. 2007) and make several unknown observations. First, we show different spectrum of infections in immunocompromised and immunocompetent patients and further point out a different profile of infections within the specific types of immunosuppression. HIV-negative patients on immunosuppressive therapies suffered mostly from infections with HSV/VZV, whilst HIV-positive patients exhibited predominantly CMV retinitis and ocular syphilis. In contrast, patients with malignancies were characterized by a lower prevalence of infections and higher prevalence of sarcoidosis. The aetiology of uveitis in patients with DM was similar to immunocompetent patients, with the exception of higher prevalence of bacterial intraocular infections in the DM patients.

So far, the comparison of uveitis causes for the different types of immunocompromised states was not performed. Previous reports studied ocular abnormalities occurring in a single cause of immunosuppression, such as after organ and/or hematologic transplantations or in HIV infections. The studies of uveitis occurring during immunosuppressive treatments for malignant and non-malignant disorders consist of case reports only.

In persons infected with HIV, CMV retinitis represented the major cause of ocular morbidity, especially in individuals with low CD4+ T cell counts (Cunningham & Margolis 1998). The incidence of CMV retinitis considerably decreased in countries with available highly active antiretroviral therapy. In HIV-infected persons with CD4+ T cell counts above 200 cells/mm³, infections still represented a major cause of uveitis

and comprised mainly syphilis and HSV/VZV infections (Rose-Nussbaumer et al. 2014). Further, the prevalence of immune recovery uveitis (IRU) is recently rising in this category of patients (Kempen et al. 2006; Sudharshan et al. 2013). Our data shows that CMV retinitis occurred in the majority of our patients with HIV infection (usually in newly diagnosed patients with acquired immunodeficiency syndrome or treatment failures). Our results also illustrate the rise of ocular syphilis as an initial indication of HIV infection, which is obviously not related to immune deficiency, but to the same route of infection. The exact number of patients with IRU in our study could not be determined as the patients were classified according to the cause of their first uveitis episode diagnosed in our department.

The prevalence of specific causes of uveitis after the organ and stem cell transplantations is not known. Several studies focused on this subject, but due to scarcity of uveitis after transplantations (approximately 2%), the number of affected patients was limited (Ng et al. 1998; Akova et al. 2006; Akerele & Lightman 2007; Chung et al. 2007). The average prevalence of CMV retinitis was less than 0.1% in large studies combining organ and hematologic transplantations (in contrast to approximately 20–30% in acquired immunodeficiency syndrome) (Ng et al. 1998; Akova et al. 2006; Akerele & Lightman 2007; Chung et al. 2007; Tabbara et al. 2009a). Patients with hematologic malignancies who underwent stem cell transplantation developed CMV retinitis in 0.02–4%; these patients are severely immunosuppressed and might represent a different category (Crippa et al. 2001; Tabbara et al. 2009b; Kim et al. 2016; Yoo et al. 2017). In our series, the majority of patients after stem cell transplants suffered from HSV/VZV infections, which is similar to patients after organ transplants and those receiving immunosuppressive treatments for other causes. However, it should be taken into account that the number of patients in specific immunocompromised groups was limited. Interestingly, most of the infections in patients undergoing transplantations occurred after the prophylaxis period, when antibacterial and antiviral drugs were already stopped. Moreover, transplantation techniques and prophylactic regimens

develop quickly overtime and recent reports are associated with declining numbers of intraocular infections (Stoyanova et al. 2014). The infection prevention in other populations undergoing immunosuppressive treatment is not well defined or not given.

The prevalence of sarcoidosis in our total series is 14%, which is slightly higher than approximately 10% in other European series and could be in part explained by a sarcoidosis centre located in our institution (Barisani-Asenbauer et al. 2012; Jones 2015). However, our series consist predominantly of patients referred for their uveitis of yet unknown cause and possibly the consistent search for sarcoidosis in our department might have influenced the high numbers of patients diagnosed with sarcoidosis. High percentage of sarcoidosis in patients with DM is striking. In patients with DM, sarcoidosis formed a most common uveitis cause (23%); the association between DM and sarcoidosis was previously noted (Hemminki et al. 2009; Martusewicz-Boros et al. 2015). Our study also demonstrates that sarcoid-reactions in malignancies might include uveitis (Balasubramaniam et al. 2015).

The anatomical classification and causes of uveitis of our study are roughly consistent with the previous large series in uveitis (Barisani-Asenbauer et al. 2012; Bajwa et al. 2015; Jones 2015; Llorenç et al. 2015; Luca et al. 2017; Zagora et al. 2017). The number of patients with anterior uveitis usually reflects the referral pattern in a given population and is commonly considered as a measure for severity of uveitis population (Tomkins-Netzer et al. 2014). The percentage of 35% of anterior uveitis in our series is somewhat lower than in most tertiary series. Low prevalence of anterior uveitis in our centre undoubtedly reflects a referral pattern in the Netherlands and reveals the severity of our uveitis patients.

Our criteria for the diagnosis of infectious uveitis were strict and presumed infections were classified as of unknown origin. Therefore, it is possible that the prevalence of infections in immunocompromised patients is even higher than 43% determined in our study. Most infections in immunocompromised patients progress quickly and may lead to irreversible blindness. It is clear that most immunocompromised patients with infectious uveitis would benefit from being treated at early stage.

As the progression can be halted with antibiotic therapy, the rapid diagnosis and treatment of immunocompromised patients is crucial for the visual outcome and might prevent permanent visual loss in these vulnerable patients. Contrary to the conventional approach, quick assessment for infections, preferably by intraocular fluid assessment, should be performed in all immunocompromised patients with uveitis. In the Netherlands, national uveitis guidelines recommend approaching uveitis in immunocompromised patients as an emergency and advise to refer patients on the same day to centres with possibilities of intraocular fluid assessment and experience in treating such complex cases. Commonly, the side effects of multi-medication and resistance to antibiotics complicate the course of the ocular disease. The concise management of immunosuppressed patients with uveitis may improve their visual outcomes with relative safety. Due to the different spectrum of uveitis causes, we believe that the future studies on uveitis should specify the number of immunosuppressed patients included.

In conclusion, our study reveals different spectrum of uveitis in immunocompetent and immunocompromised individuals and demonstrates that distinct types of immunosuppression are associated with different causes of uveitis. Specifically, we show that a rapid assessment for viral and other infectious causes should be performed in all immunosuppressed subjects.

References

- Acharya NR, Browne EN, Rao N & Mochizuki M; International Ocular Sarcoidosis Working Group (2018): Distinguishing Features of Ocular Sarcoidosis in an International Cohort of Uveitis Patients. *Ophthalmology* **125**: 119–126.
- Akerele T & Lightman S (2007): Ocular complications in heart, lung and heart-lung recipients. *Br J Ophthalmol* **91**: 310–312.
- Akova YA, Altan-Yaycioglu R, Yilmaz G, Azap OK & Haberal M (2006): Opportunistic posterior uveal infections in renal transplant patients. *Transplant Proc* **38**: 1348–1353.
- Bajwa A, Osmanzada D, Osmanzada S, Khan I, Patrie J, Xin W & Reddy AK (2015): Epidemiology of uveitis in the mid-Atlantic United States. *Clin Ophthalmol* **9**: 889–901.
- Balasubramaniam SC, Salomão DR, Davies JB, Ramsay RC, Habermann TM, Chow GK, Boorjian SA & Pulido JS (2015): Paraneoplastic sarcoid-like reactions and the eye. *Retina* **35**: 789–797.
- Barisani-Asenbauer T, Maca SM, Mejdoubi L, Emminger W, Machold K & Auer H (2012): Uveitis- a rare disease often associated with systemic diseases and infections- a systematic review of 2619 patients. *Orphanet J Rare Dis* **7**: 57.
- Berrou J, Fougeray S, Venot M, Chardiny V, Gautier JF, Dulphy N, Toubert A & Peraldi MN (2013): Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. *PLoS ONE* **25**: e62418.
- Bonten MJM, Huijts SM, Bolkenbaas M et al. (2015): Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* **372**: 1114–1125.
- Chung H, Kim KH, Kim JG, Lee SY & Yoon YH (2007): Retinal complications in patients with solid organ or bone marrow transplantations. *Transplantation* **83**: 694–699.
- Crippa F, Corey L, Chuang E L. et al. (2001): Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. *Clin Infect Dis* **32**: 214–219.
- Cunningham ET Jr & Margolis TP (1998): Ocular manifestations of HIV infection. *N Engl J Med* **339**: 236–244.
- Graham C, Chooniedass R, Stefura WP et al. (2017): *In vivo* immune signatures of healthy human pregnancy: inherently inflammatory or anti-inflammatory? *PLoS ONE* **12**: e0177813.
- Hemminki K, Li X, Sundquist J & Sundquist K (2009): Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia* **52**: 1820–1828.
- Herbert CP, Rao NA & Mochizuki M; members of Scientific Committee of First International Workshop on Ocular Sarcoidosis (2009): International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm* **17**: 160–169.
- Hodgeson K, Morris J, Bridson T, Govan B, Rush C & Ketheesan N (2015): Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. *Immunology* **144**: 171–185.
- Jabs DA, Nussenblatt RB & Rosenbaum JT; STANDARDIZATION OF UVEITIS NOMENCLATURE(SUN) WORKING GROUP (2005): Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* **140**: 509–516.
- Jafar N, Edriss H & Nugent K (2016): The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci* **351**: 201–211.
- Jones NP (2015): The Manchester Uveitis Clinic: the first 3000 patients—epidemiology and casemix. *Ocul Immunol Inflamm* **23**: 118–126.
- Kempen JH, Min YI, Freeman WR, Holland GN, Friedberg DN, Dieterich DT & Jabs DA; Studies of Ocular Complications of AIDS Research Group (2006): Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology* **113**: 684–694.
- Kim T, Lee YM, Lee SO et al. (2016): Differences of cytomegalovirus diseases between kidney and hematopoietic stem cell transplant recipients during preemptive therapy. *Korean J Intern Med* **31**: 961–970.
- Llorenç V, Mesquida M, Sainz de la Maza M et al. (2015): Epidemiology of uveitis in a Western urban multiethnic population. The challenge of globalization. *Acta Ophthalmol* **93**: 561–567.
- Luca C, Raffaella A, Sylvia M et al. (2017): Changes in patterns of uveitis at a tertiary referral center in Northern Italy: analysis of 990 consecutive cases. *Int Ophthalmol* **38**(1): 133–142.
- Martusewicz-Boros MM, Boros PW, Wiatr E & Roszkowski-Sliż K (2015): What comorbidities accompany sarcoidosis? A large cohort (n = 1779) patients analysis. *Sarcoidosis Vasc Diffuse Lung Dis* **32**: 115–120.
- Ng P, McCluskey P, McCaughan G, Glanville A, MacDonald P & Keogh A (1998): Ocular complications of heart, lung, and liver transplantation. *Br J Ophthalmol* **82**: 423–428.
- Robinson DP & Klein SL (2012): Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. *Horm Behav* **62**: 263–271.
- Rose-Nussbaumer J, Goldstein DA, Thorne JE et al. (2014): Uveitis in human immunodeficiency virus-infected persons with CD4 + T-lymphocyte count over 200 cells/mL. *Clin Exp Ophthalmol* **42**: 118–125.
- Stoyanova EI, Riemens A, Lokhorst HM, te Boome L & Rothova A (2014): Absence of intraocular infections after hematopoietic stem cell transplantation at a single center: the experience with current preventive regimens. *Ocul Immunol Inflamm* **22**: 116–120.
- Sudharshan S, Kaleemunnisha S, Banu AA et al. (2013): Ocular lesions in 1,000 consecutive HIV-positive patients in India: a longterm study. *J Ophthalmic Inflamm Infect* **3**: 2.
- Tabbara KF, Qahtani FM & Wedin KL (2009a): Infections following organ transplantation. *Ophthalmology* **116**: 1232–1234.
- Tabbara KF, Al-Ghamdi A, Al-Mohareb F et al. (2009b): Ocular findings after allogeneic hematopoietic stem cell transplantation. *Ophthalmology* **116**: 1624–1629.
- Tchernev G, Tana C, Schiavone C, Cardoso JC, Ananiev J & Wollina U (2014): Sarcoidosis vs. Sarcoid-like reactions: The Two Sides of the same Coin?. *Wien Med Wochenschr* **164**: 247–259.
- Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SR, Joshi L et al. (2014): Long-term clinical outcome and causes of vision loss in patients with uveitis. *Ophthalmology* **121**: 2387–2392.
- Westeneng AC, Rothova A, de Boer JH & de Groot-Mijnes JD (2007): Infectious uveitis in immunocompromised patients and the diagnostic value of polymerase chain reaction and Goldmann-Witmer coefficient in aqueous analysis. *Am J Ophthalmol* **144**: 781–785.
- Yoo YS, Na KS, Shin JA, Park YH & Lee JW (2017): Posterior eye segment complications related to allogeneic hematopoietic stem cell transplantation. *Retina* **37**: 135–143.
- Zagora SL, Symes R, Yeung A, Yates W, Wakefield D & McCluskey PJ (2017): Etiology and Clinical Features of Ocular Inflammatory Diseases in a Tertiary Referral Centre in Sydney, Australia. *Ocul Immunol Inflamm* **25**(sup1): S107–S114.

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