General introduction and aims of this thesis
GENERAL INTRODUCTION

Background of uveitis

Uveitis refers to the inflammation of the uvea, the middle vascular coat (iris, ciliary body and choroid) of the eye. It is a large group of diverse diseases affecting also the retina, optic nerve and vitreous. The term uvea derives from the Latin word for ‘grape’, as defined by early anatomists based on the tissue color and geometry. Uveitis is the most common cause of inflammatory eye disease and an important cause of blindness and visual impairment. It affects predominantly people of working age, but it may affect individuals of any age. Uveitis in children aged younger than 16 years is relatively uncommon accounting for only 5% to 10% of cases, for example patients with juvenile idiopathic arthritis (JIA). The annual incidence of uveitis worldwide is between 17 and 52 per 100,000 people, and the prevalence is 38 to 714 cases per 100,000 people.

The standardization of uveitis nomenclature (SUN) working group has developed a process of standardizing the methods for reporting clinical data in the field of uveitis. According to the SUN working group, the anatomic classification of uveitis should be used as a framework for subsequent work on diagnostic criteria for specific uveitic syndromes and the classification of uveitis entities should be on the basis of the location of the inflammation and not on the presence of structural complications. Uveitis is classified anatomically into anterior, intermediate, posterior and panuveitis. Anterior uveitis (AU) is the most common type of uveitis.

Uveitis can also be classified etiologically in traumatic, immunologic (non-infectious, e.g. associated with HLA-B27 positivity, Behçet’s disease, sarcoidosis), infectious (e.g. herpetic, toxoplasmosis, rubella) and masquerade (e.g. lymphoma, paraneoplastic syndromes). In addition, there is a large group of patients with idiopathic uveitis. Uveitis associated with HLA-B27 positivity can be associated with systemic disease (e.g. ankylosing spondylitis, reactive arthritis), but a study by Zagora et al. showed that in approximately 80% there is no associated systemic disease. It is important to understand that all these different uveitis entities have a different clinical course, dissimilar complications, need other treatment strategies and vary in prognosis.

Anterior uveitis

As mentioned earlier, AU is the most common type of uveitis, accounting for 50% to 60% of all uveitis cases in tertiary referral centers and 90% in primary care settings. In AU, the primary site of inflammation is the anterior chamber and includes iritis, iridocyclitis and anterior cyclitis. The most common causes of AU are idiopathic (37.8%), seronegative HLA-B27-associated arthropathies (21.6%), JIA (10.8%) herpetic uveitis (9.7%), sarcoidosis (5.9%) and Fuch’s heterochromic iridocyclitis (5.0%). In this thesis, we will discuss two types of AU, HLA-B27 associated AU, the most common non-infectious form, and herpetic AU, the most common infectious form.
HLA-B27 associated anterior uveitis

Human leukocyte antigen B27 (HLA-B27) is a class I surface antigen encoded by the B locus in the major histocompatibility complex (MHC) on chromosome 6 and presents antigenic peptides to T cells. HLA-B27 is strongly associated with systemic inflammatory diseases referred to as spondylo-arthropathies. Associated systemic diseases are nonspecific arthropathy, ankylosing spondylitis, reactive arthritis, inflammatory bowel disease (Crohn’s disease, ulcerative colitis) and psoriatic arthropathy. The most prevalent is ankylosing spondylitis.

Ankylosing spondylitis is a chronic systemic disease of unknown cause, characterized primarily by inflammation of both sacroiliac joints and the spine, and also by a variety of extra-articular manifestations. AU is the most common extra-articular manifestation, it occurs in approximately 25% of patients, either before the onset of ankylosing spondylitis or at some point thereafter. Rothova et al. showed that the diagnosis ankylosing spondylitis was established before the onset of uveitis in 16 of 41 (39%) patients and during the uveitis work-up in the remaining 25 (61%).

Having the HLA-B27 antigen is a genetic risk factor for developing AU, as about 55% of Caucasian patients with AU are HLA-B27 positive compared to 8% to 10% of the general Caucasian population. It is important to know that not all HLA-B27 positive individuals develop AU.

HLA-B27 associated AU predominantly affects young adults (mean age of about 35 years), and there is a male preponderance (3:1). The most characteristic ocular manifestation associated with HLA-B27 positivity consists of unilateral AU of acute onset. The uveitis is typically recurrent with a full remission between the episodes. Presentation is unilateral, bilateral or alternating. The features indicative of HLA-B27 associated AU are intense cellular reaction, fibrine, hypopyon, posterior synechiae and fine whitish-gray keratic precipitates.

Herpetic anterior uveitis

Herpetic AU is the most frequently observed form of infectious AU, and it is usually unilateral. Eight herpes viruses are found in humans: herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella zoster virus (VZV), human cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes viruses 6, 7 and 8 (HHV-6, HHV-7 and HHV-8). The three main herpes viruses involved in ocular disease are HSV, VZV and CMV. Although HSV, VZV and CMV all belong to the herpes family, and have certain clinical features in common, they differ in significant aspects. Characteristics like dermatitis, keratitis, elevated intraocular pressure (IOP) and iris sector atrophy are seen in herpetic AU. All herpes viruses tend to establish latent or clinically silent infections in the host and can reactivate in response to certain stimuli.

Herpes simplex virus and varicella zoster virus

Nearly 100% of individuals older than 60 years of age harbor HSV in their trigeminal ganglia. The infection is spread by direct contact with lesions or secretions of other infected individuals, but...
the most common source of infection is exposure to virus shed asymptomatically in mucosal secretions of latently infected individuals. VZV causes two distinct systemic diseases. Varicella, or chickenpox, is seen in primary infection. Zoster occurs after reactivation of the persistent latent VZV infection in the sensory ganglia. Patients with VZV uveitis tend to be older than patients with HSV AU, as VZV uveitis is usually a result of reactivation of latent VZV in older individuals.

The features indicative of a herpetic (HSV/VZV) AU include elevated IOP, iris atrophy (usually patchy or diffuse) or diffuse stellate keratic precipitates. A sudden increase in IOP can be caused by trabeculitis, an inflammation of the trabecular meshwork endothelium. Iris atrophy can be a result of ischemic necrosis by occlusive vasculitis and may be associated with a dilated and/or distorted pupil.

Herpetic AU may appear with or without corneal lesions (keratitis). The presence of corneal scars or corneal hypo-aesthesia especially with sector iris atrophy is suggestive of HSV or VZV infection. Corneal scars caused by keratitis can have a significant impact on visual acuity (VA). In cases with isolated anterior chamber involvement, without other characteristics, the causative agent involved may be difficult to determine, in these cases an aqueous analysis is needed.

Complications in anterior uveitis

AU can lead to several ocular complications, such as acute complications (e.g. cystoid macular oedema (CMO), papillitis, elevated IOP, keratitis) and complications that develop in the course of the disease (e.g. glaucoma, cataract). Prominent textbooks mainly focus on diagnosis of and therapy for different uveitis entities and only refer to entity-related (long-term) prognosis and complications in a general way. In addition, there is a broad variation in reported rates of ocular complications. Factors contributing to this variation include non-uniform definitions and variable follow-up times, which is a well-recognized problem in the field of uveitis. A few of these complications will be discussed in more detail.

Ocular hypertension and glaucoma

The term elevated IOP should be used for those situations where there is an IOP above a defined normal range (e.g. 21 mmHg) or when there is an increase in IOP from baseline during a study with longitudinal data. The term glaucoma should not be considered synonymous with elevated IOP, but it should be reserved for those situations where there is either observed glaucomatous disk damage or demonstrated visual field loss.

Elevated IOP is reported to develop in 46-51% and secondary glaucoma in 2-54% in herpetic AU patients. As said before, in herpetic AU a sudden increase of the IOP is often caused by trabeculitis and thus typically occurs at the onset of a uveitis episode. With regard to HLA-B27 associated AU, elevated IOP is reported in 5 to 20% and secondary glaucoma in 0 to 12% of patients. This typically develops in the course of the disease, whereas IOP at the onset of a
uveitis episode can even be low due to inflammation of the ciliary body and decreased aqueous production.\textsuperscript{30} In spite of those differences, some pathogenic mechanisms causing an increase in IOP may be quite similar, such as trabeculitis, the accumulation of inflammatory cells and debris in the trabecular meshwork, and structural changes in the outflow system due to prolonged inflammation. In both herpetic and HLA-B27 associated AU, elevated IOP and secondary glaucoma can be caused by the use of corticosteroids.\textsuperscript{11} The exact mechanism hereof is not fully understood, but it is possibly due to the deposition of mucopolysaccharides in the trabecular meshwork.\textsuperscript{31}

Cataract
Corticosteroids are the mainstay of therapy for patients with uveitis. One of the most common and clinically significant ocular complication of the use of corticosteroids is the development of cataract.\textsuperscript{11} Cataract is a major cause of vision impairment in the general population worldwide and is defined as the loss of transparency of the eye lens.\textsuperscript{32,33} The most common type of cataract caused by corticosteroid use is posterior subcapsular cataract, this is located in the posterior cortical layer and is usually axial.\textsuperscript{11,34} The longer the duration of corticosteroid use and the higher the dose, the faster the cataract develops.\textsuperscript{11} Cataract development in patients with uveitis can also result from chronic inflammation.\textsuperscript{35} Cataract is reported to develop in 13 to 32\% in herpetic AU patients.\textsuperscript{21,26,27} With regard to HLA-B27 associated AU, cataract is reported in 5 to 28\%.\textsuperscript{18,28,29}

Other ocular complications
In herpetic AU, keratitis / corneal involvement is seen in 25 to 57\% and posterior synechiae in 26 to 40\% of eyes.\textsuperscript{21,26,27} Other typical complications related to herpetic AU are ocular pareses, pathological mydriasis and to a lesser extent ptosis.\textsuperscript{36,37} With regard to HLA-B27 associated AU posterior synechiae are seen in 8 to 52\% and CMO in 9 to 31\% of patients.\textsuperscript{18,28,29}

Visual acuity in anterior uveitis
Rothova et al. showed that 35\% of all uveitis patients in the Western society are significantly visually impaired or blind. Bilateral loss of VA developed in 10\% and unilateral loss of vision occurred in an additional 25\% of all patients with uveitis. The main cause of visual impairment was CMO.\textsuperscript{38} Visual loss in uveitis occurs most commonly in patients with panuveitis, CMO and cataract, either individually or in combination.\textsuperscript{2}

Tugal-Tutkun et al. report that final VA in herpetic AU was worse than 0.5 in 17\% (19/114) of the involved eyes and was due to lens opacity in two and corneal scars in 17 eyes. Patients with only iridocyclitis had no permanent visual loss. Median follow-up period was 22.4 months.\textsuperscript{27} In another study by Wensing et al. VA in herpetic AU (HSV and VZV) was worse than 0.1 in 6\% (1/18) and 0.1 to 0.4 in 6\% (1/18) at three years follow-up.\textsuperscript{26}

Reports on final VA outcomes in HLA-B27 associated AU differ, since Tuncer et al. reported
relatively good VA outcomes, since 9% (5/59) of eyes had a Snellen VA between 0.1 and 0.4 and none had a Snellen VA of less than 0.1 after a median follow-up period of 35.1 months. Power et al. reported less favorable VA outcomes. In the latter study, 9% (26/291) of eyes became legally blind after a median follow-up period of 14.6 months in patients without and 19.3 months in patients with systemic disease.

**Quality of life in uveitis**

The assessment of health-related quality of life (QOL) has been increasingly recognized as providing an important marker of health outcome in the general population and for those with chronic or life-threatening conditions. The definition of the World Health Organization of QOL, is a state of complete physical, mental and social well-being. QOL can be affected by the uveitis and ocular complications, VA, treatment and also by an associated systemic disease. As uveitis often afflicts the young adult population in their most productive years of life, the personal and population burden of this sight-threatening disease is significant. Proper diagnosis and treatment of uveitis and the possible systemic condition can enormously enhance QOL.

Most studies evaluated vision-related quality of life (VR-QOL) in heterogeneous groups of uveitis patients. Schiffman et al. showed that uveitis patients have a poorer visual functioning and a lower general health status compared to healthy subjects. In addition, some studies looked at VR-QOL in specific uveitis patient groups and found that VR-QOL is impaired in patients with birdshot chorioretinopathy, Behçet’s disease and adult patients with juvenile idiopathic arthritis and a history of uveitis. The National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) is frequently used to measure the VR-QOL. It is a self-administered questionnaire and consists of a base set of 25 vision-targeted questions representing 11 vision-related subscales, plus an additional single-item general health rating question (see appendix).

**Aims and the outline of this thesis**

The main objective of this thesis is to get a better insight in the ocular characteristics, ocular complications, VA outcomes and QOL of patients with herpetic and HLA-B27 associated AU. By giving entity-specific information on the most common representatives of non-infectious (HLA-B27 associated) and infectious (herpetic) AU, we hope to contribute to a more personalized care of uveitis patients. In all our studies, we use the guidelines for uniform reporting in uveitis developed by the SUN working group to enable comparisons with future studies in the field.

Chapter 2 gives information on the rate of complications, ocular characteristics and the visual prognosis in herpetic compared to HLA-B27 associated AU, which are relatively large and homogeneous AU patient groups at our center. Chapter 3 describes the incidence of elevated IOP and secondary glaucoma in herpetic AU (HSV and VZV). In Chapter 4 we evaluate whether ocular and patient characteristics differ between unilateral and bilateral HLA-B27 associated AU with or without systemic disease. Chapter 5 aims to describe the VR-QOL and the prevalence
and severity of depression in herpetic (HSV and VZV) AU. In chapter 6, we evaluate the VR-QOL in a group of patients with HLA-B27 associated AU. The most important findings are summarized and discussed in chapters 7 and 8.
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