Herpetic and HLA-B27 associated anterior uveitis

Ocular complications, prognosis and vision-related quality of life

Lisette Hoeksema

Colophon

Cover: Véronique Baur
Graphic design: Douwe Oppewal (www.oppewal.nl)
Printed by: NetzoDruk, Groningen (www.netzodruk.nl)

ISBN printed version: 978-94-034-1718-9
ISBN digital version: 978-94-034-1717-2

Printing of these thesis was financially supported by the University Medical Center Groningen, University of Groningen and Prof. Mulder Stichting

rijksuniversiteit
groningen

Herpetic and HLA-B27 associated anterior uveitis

Ocular complications, prognosis and vision-related quality of life

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 1 juli 2019 om 11.00 uur

door

Lisette Hoeksema

geboren op 20 november 1984
te Delfzijl

Promotor
Prof. dr. J.M.M. Hooymans

Copromotor
Dr. L.I. Los

Beoordelingscommissie
Prof. dr. A. Rothova
Prof. dr. J. Boer de
Prof. dr. H. Bootsma

Table of contents

1

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.[1,2] The term uvea derives from the Latin word for 'grape', as defined by early anatomists based on the tissue color and geometry.[3] 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.[1,2] 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)*.[4] 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.[1]

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.[5] Uveitis is classified anatomically into anterior, intermediate, posterior and panuveitis. Anterior uveitis (AU) is the most common type of uveitis.[6,7]

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.[8] 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.[9] In AU, the primary site of inflammation is the anterior chamber and includes iritis, iridocyclitis and anterior cyclitis.[5] 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%).[10] 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.[11] The most prevalent is ankylosing spondylitis.[12]

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.[11] 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%).[13]

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.[14] It is important to know that not all HLA-B27 positive individuals develop AU.[15]

HLA-B27 associated AU predominantly affects young adults (mean age of about 35 years), and there is a male preponderance (3:1).[16] The most characteristic ocular manifestation associated with HLA-B27 positivity consists of unilateral AU of acute onset.[12] The uveitis is typically recurrent with a full remission between the episodes.[16] Presentation is unilateral, bilateral or alternating.[11] The features indicative of HLA-B27 associated AU are intense cellular reaction, fibrine, hypopyon, posterior synechiae and fine whitish-gray keratic precipitates.[17-19]

Herpetic anterior uveitis

Herpetic AU is the most frequently observed form of infectious AU, and it is usually unilateral.[20,21] 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).[11] 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.[22] All herpes viruses tend to establish latent or clinically silent infections in the host and can reactivate in response to certain stimuli.[11]

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.[11] 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.[21,23]

The features indicative of a herpetic (HSV/VZV) AU include elevated IOP, iris atrophy (usually patchy or diffuse) or diffuse stellate keratic precipitates.[22] A sudden increase in IOP can be caused by trabeculitis, an inflammation of the trabecular meshwork endothelium.[11] Iris atrophy can be a result of ischemic necrosis by occlusive vasculitis and may be associated with a dilated and/or distorted pupil.[11,24]

Herpetic AU may appear with or without corneal lesions (keratitis).[11] The presence of corneal scars or corneal hypo-aesthesia especially with sector iris atrophy is suggestive of HSV or VZV infection.[22] 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.[11,25] 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.[5] 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.[5]

Elevated IOP is reported to develop in 46 to 51% and secondary glaucoma in 2 to 54% in herpetic AU patients.[21,26,27] 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.[11] With regard to HLA-B27 associated AU, elevated IOP is reported in 5 to 20% and secondary glaucoma in 0 to 12% of patients.[18,28,29] 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.[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.[11] The exact mechanism hereof is not fully understood, but it is possibly due to the deposition of mucopolysaccharides in the trabecular meshwork.[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.[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.[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.[11,34] The longer the duration of corticosteroid use and the higher the dose, the faster the cataract develops.[11] Cataract development in patients with uveitis can also result from chronic inflammation.[35] Cataract is reported to develop in 13 to 32% in herpetic AU patients.[21,26,27] With regard to HLA-B27 associated AU, cataract is reported in 5 to 28%.[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.[21,26,27] Other typical complications related to herpetic AU are ocular pareses, pathological mydriasis and to a lesser extent ptosis.[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.[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.[38] Visual loss in uveitis occurs most commonly in patients with panuveitis, CMO and cataract, either individually or in combination.[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.[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.[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.[28] 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.[29]

Quality of life in uveitis

The assessment of health-related quality of life (QOL) has been increasingly recognised 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.[39] 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.[1] Proper diagnosis and treatment of uveitis and the possible systemic condition can enormously enhance QOL.[11]

Most studies evaluated vision related quality of life (VR-QOL) in heterogenous groups of uveitis patients.[40-42] Schiffman et al. showed that uveitis patients have a poorer visual functioning and a lower general health status compared to healthy subjects.[40] 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.[43-45] 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).[46,47]

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**.

REFERENCES

1. Wakefield D, Chang JH. Epidemiology of uveitis. Int Ophthalmol Clin. 2005 Spring;45:1-13.
2. Durrani OM, Meads CA, Murray PI. Uveitis: A Potentially Blinding Disease. Ophthalmologica 2004;218:223–236.
3. Grillo A, Levinson RD, Gordon LK. Practical Diagnostic Approach to Uveitis. Expert Rev Ophthalmol. 2011;6:449-459.
4. Cunningham ET Jr. Uveitis in children. Ocul Immunol Inflamm. 2000;8:251–261.
5. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
6. Huang JJ, Gaudio PA. Ocular inflammatory disease and uveitis manual: diagnosis and treatment. Philadelphia, Wolters Kluwer, Lippincott Williams & Wilkins;2010.
7. Riordan – Eva P, Emmett T, Cunningham Jr. Vaughan & Asbury's General Ophthalmology. 18th edition, New York, The McGraw-Hill Companies. Chapter 7 (ebook);2011.
8. Zagora SL Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, AustraliaCorrespondencesophia.zagora@gmail.com , Symes R Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Yeung A Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Yates W Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Wakefield S School of Medical Sciences, Faculty of Medicine University of NSW, Sydney, NSW, Australia, McCluskey PJ Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia. Etiology and Clinical Features of Ocular Inflammatory Diseases in a Tertiary Referral Centre in Sydney, Australia. Ocul Immunol Inflamm. 2017;25:S107-S114.
9. Chang JH, Wakefield D. Uveitis: a global perspective. Ocul Immunol Inflamm. 2002;10: 263–279.
10. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. Arch Ophthalmol. 1996;114:593-599.
11. Foster CS, Vitale AT. Diagnosis and Treatment of Uveitis. 1st edition, Philadelphia, Pennsylvania, W. B. Saunders Company;2002.
12. Rosenbaum JT. Uveitis in spondyloarthritis including psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. Clin Rheumatol. 2015;34:999–1002.
13. Rothova A, Buitenhuis HJ, Meenken C, et al. Uveitis and systemic disease. Br J Ophthalmol. 1992;76:137–141.
14. Brewerton DA, Caffrey M, Nicholls A, et al. Acute anterior uveitis and HL-A 27. Lancet. 1973;2:994–996.
15. Wakefield D, Montanaro A, McCluskey P. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 1991;36:223–232.
16. Rothova A, van Veenedaal WG, Linssen A, et al. Clinical features of acute anterior uveitis. Am J Ophthalmol. 1987;103:137–145.
17. Mapstone R, Woodrow JC. HL-A 27 and acute anterior uveitis. Br J Ophthalmol. 1975;59:270–275.
18. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. Am J Ophthalmol. 1996;121:47–56.
19. Monnet D, Breban M, Hudry C, et al. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. Ophthalmology. 2004;111:802–809.
20. Jakob E, Reuland MS, Mackensen F, et al. Uveitis subtypes in a German interdisciplinary uveitis center—analysis of 1916 patients. J Rheumatol. 2009;36:127–136.
21. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis. A clinical evaluation and comparison. Ophthalmology 2002; 109:1532–1537.
22. Jap A, Chee SP. Viral anterior uveitis. Curr Opin Ophthalmol. 2011;22: 483-488.
23. Van der Lelij A, Ooijman FM, Kijlstra A, Rothova A. Anterior uveitis with sectoral iris atrophy in the absence of keratitis: a distinct clinical entity among herpetic eye diseases. Ophthalmology 2000; 107:1164–1170.
24. Goldstein DA, Mis AA, Oh FS, Deschenes JG. Persistent pupillary dilation in herpes simplex uveitis. Can J Ophthalmol 2009; 44:314–316.
25. Nussenblatt RB, Whitcup SM. Uveitis, Fundamentals and Clinical Practice. 4th edition, MOSBY Elsevier; 2010.
26. Wensing B, Relvas LM, Caspers LE, et al. Comparison of rubella virus- and herpes virus-associated anterior uveitis: clinical manifestations and visual prognosis. Ophthalmology. 2011;118:1905-1910.
27. Tugal-Tutkun I, Otu¨ k-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: a retrospective study of 111 cases. Int Ophthalmol 2010; 30:559–565.
28. Tuncer S, Adam YS, Urgancioglu M, et al. Clinical features and outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis in a Turkish patient population. Ocul Immunol Inflamm. 2005;13:367-373.

29. Power WJ, Rodriguez A, Pedroza-Seres M, et al. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998;105:1646-1651.
30. Pathanapitoon K, Dodds EM, Cunningham ET Jr, Rothova A. Clinical Spectrum of HLA-B27-associated Ocular Inflammation. Ocul Immunol Inflamm. 2017;25:569-576.
31. Francois J. The importance of the mucopolysaccharides in intraocular pressure regulation. Invest Ophthalmol. 1975;14:173-176.
32. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol.* 2012;96:614–618.
33. Lovicu FJ, Shin EH, McAvoy JW. Fibrosis in the lens. Sprouty regulation of TGF**β**-signaling prevents lens EMT leading to cataract. Exp Eye Res. 2016;142:92-101.
34. Basic Clinical Science Course of the American Academy of Ophthalmology. Section 11. 2011 - 2012. Page 42-43.
35. Jancevski M, Foster CS. Cataracts and uveitis. Curr Opin Ophthalmol. 2010;21:10-14.
36. Marsh RJ, Dulley B, Kelly V. External ocular motor palsies in ophthalmic zoster: a review. Br J Ophthalmol. 1977;61:677-682.
37. Sekizawa T, Nakamura S, Kogure K, et al. Idiopathic third cranial nerve palsy associated with herpes simplex virus infection. Br Med J. 1987;295:813.
38. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, et al. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332–336.
39. World Health Organization: The constitution of the World Health Organization. WHO Chron. 1947;1:29.
40. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol. 2001;119:841-849.
41. Qian Y, Glaser T, Esterberg E, Acharya NR. Depression and visual functioning in patients with ocular inflammatory disease. Am J Ophthalmol. 2012;153:370-378.
42. Naik RK, Gries KS, Rentz AM, Kowalski JW, Revicki DA. Psychometric evaluation of the National Eye Institute Visual Function Questionnaire and Visual Function Questionnaire Utility Index in patients with non infectious intermediate and posterior uveitis. Qual Life Res. 2013;22:2801-2808.
43. Kuiper JJ, Missotten T, Baarsma SG, Rothova A. Vision-related quality of life in patients with birdshot chorioretinopathy. Acta Ophthalmol. 2013;91:e329-331.
44. Fabiani C, Vitale A, Orlando I, et al. Quality of life impairment in Behçet›s disease and relationship with disease activity: a prospective study. Intern Emerg Med. 2017;12:947-955.
45. Haasnoot AJW, Sint Jago NFM, Tekstra J, de Boer JH. Impact of Uveitis on Quality of Life in Adult Patients With Juvenile Idiopathic Arthritis. Arthritis Care Res. 2017;69:1895-1902.
46. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol. 1998;116:1496-1504.
47. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119:1050-1058.

2

Visual prognosis and ocular complications in herpetic versus HLA-B27- or ankylosing spondylitis-associated anterior uveitis

Lisette Hoeksema & Leonoor I Los

Ocul Immunol Inflamm. 2016; 24: 302-312

ABSTRACT

Purpose: To investigate the visual prognosis and ocular complications in patients with herpetic versus HLA-B27 associated anterior uveitis (AU).

Methods: This was a retrospective, observational study conducted at the ophthalmology department of the University Medical Center of Groningen. Sixty-two herpetic and 113 HLA-B27 associated AU patients were included. The main outcome measures were visual acuity and ocular complications.

Results: Visual acuity over time was significantly lower in herpetic as compared to HLA-B27 AU, mainly due to corneal scarring. The incidence rate of any ocular complication was higher in herpetic AU compared to HLA-B27 associated AU (0.140/EY versus 0.076/EY, p=<0.001), which was mainly due to glaucoma (0.033/EY versus 0.004/EY, p<0.001) and cataract (0.059/EY versus 0.023/EY, p<0.001).

Conclusions: The most prominent finding was a worse visual prognosis in herpetic AU, which is probably related to higher prevalences of corneal scarring and glaucoma. In addition, herpetic AU patients have more ocular complications overall.

INTRODUCTION

Anterior uveitis (AU) is the most common type of uveitis.[1,2] Complications of uveitis can lead to irreversible loss of visual functioning.[1] Previous studies showed that 35% of uveitis patients in the Western society are significantly visually impaired or blind.[3] It is well accepted that identifying the right cause of the uveitis at an early stage of the disease is important, in order to customize treatment strategies, prevent complications that affect visual acuity (VA) and inform the patient in a correct way.

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.[4,5] Some information on clinical features and prognosis of herpes simplex virus (HSV) AU, varicella zoster virus (VZV) AU and herpetic uveitis can be found in publications e.g. by Wensing et al, Tugal-Tutkun et al. and Miserocchi et al.[6-8] Cataract is reported to develop in 13 to 32%, elevated intraocular pressure in 46 to 51%, secondary glaucoma in 2 to 54%, keratitis / corneal involvement in 25 to 57% and posterior synechiae in 26 - 40% of eyes.[6-8] Other typical complications related to herpetic AU are ocular pareses, pathological mydriasis and to a lesser extent ptosis.[9,10] Reports on VA in herpetic AU indicate that 11/48 (23%) of eyes had a Snellen VA ≤ 0.4 and 26/68 (38%) of eyes had a VA ≥ 20/40 at onset.[6,8] VA remains relatively good during follow-up, since 2/18 (11%) of eyes had a Snellen VA ≤ 0.4 at three years follow-up and 95/114 (83%) of eyes had a Snellen VA > 0.5 at a median follow-up of 22.4 months.[6,7]

With regard to HLA-B27 AU, cataract is reported in 5 to 28%, elevated intraocular pressure in 5 to 20%, secondary glaucoma in 0 to 12%, posterior synechiae in 8 to 52% and cystoid macular edema (CME) in 9 to 31% of eyes.[11-13] Reports on final VA outcomes differ, since Tuncer et al. reported relatively good VA outcomes (5/59 (9%) of eyes had a Snellen VA between 0.1 – 0.4 and none had a Snellen VA < 0.1)[11], whereas Power et al. reported less favorable VA outcomes. In the latter study, 26/291 (9%) of eyes became legally blind.[12]

Factors contributing to the differences in reported rates of ocular complications probably include non-uniform definitions and variable follow-up times, which is a well-recognized problem in the field of uveitis.[14]

The present study aims to give information on the rate of complications and the visual prognosis in two relatively large and homogeneous AU patient groups. By using the guidelines for uniform reporting in uveitis studies as developed by the SUN working group[14], we hope to minimize drawbacks inherent in retrospective studies. We compare main outcome measures between infectious AU caused by HSV or VZV and non-infectious HLA-B27 or ankylosing spondylitis associated AU. These are common causes of uveitis in the Western world and these groups comprise the largest defined AU groups at our center, with a relatively long follow-up time. These

groups of AU have a very different pathogenesis, but can lead to similar ocular complications and loss of VA.

METHODS

Ethics Statement

The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study.

Patients

Patients diagnosed with either herpetic or HLA B27 / ankylosing spondylitis associated AU were included in this study. They were selected from an existing database, containing uveitis patients treated at the ophthalmology clinic of the University Medical Center Groningen, which is a tertiary referral center. There was no selection on the upper or lower limit for age. In patients with bilateral anterior uveitis, we included the first eye diagnosed with anterior uveitis.

For the herpetic group, we included patients with AU based on a herpes infection (HSV/VZV). The diagnosis was made by clinical presentation or a positive anterior chamber tap for local antibody production or the presence of virus DNA by PCR. Patients without a performed anterior chamber tap had to have AU in combination with at least one clinical characteristic associated with herpetic AU: (1) keratitis - dendritic herpes branch - followed by AU, (2) elevated intraocular pressure (IOP) at presentation, (3) iris transillumination defects developing over time and/or (4) clear facial varicella zoster infection (ophthalmic nerve) with subsequent kerato-uveitis (Table 1). Elevated IOP at presentation could be the only observed clinical characteristic (n=3 patients), but only if it had been present at the start of multiple uveitis episodes. Facial skin lesions (ophthalmic nerve) were considered as a strong indication of VZV-related uveitis. Keratitis can be associated with both HSV and VZV infection, but larger herpetic corneal branches were considered indicative of HSV. For the HLA-B27 or ankylosing spondylitis group, we included patients with AU associated with HLA-B27 positivity or with ankylosing spondylitis diagnosed by a rheumatologist.

Patients were excluded when the cause of the AU was not certain or multiple possible causes for uveitis were identified, or there was too much missing data.

Eventually, 62 patients with herpetic AU and 113 patients with HLA-B27 or ankylosing spondylitis associated AU were included for the retrospective study. Patients with unilateral AU (i.e. excluding bilateral as well as alternating AU) were invited for a single visit to our outpatient department to verify the present state (n=111 patients). In this design, the fellow eye could serve as an internal control for ocular pareses, pathological mydriasis and ptosis. Not all unilateral AU

patients participated in the study for the present state: some patients were deceased (n=5), others refused participation (n=22), some could not be reached (n=16) and some did not attend their appointment (n=6). Thirty-three patients with herpetic AU and 29 patients with HLA-B27 or ankylosing spondylitis associated AU were included for evaluating the present state. These participants signed an informed consent form. Described research adhered to the tenets of the Declaration of Helsinki.

Data

For the retrospective study, we used patients' records. The following information was gathered: age at the time of first uveitis episode (further referred to as "onset"), gender, Snellen VA at onset, at specific time points during follow-up and at the end of follow-up, date of first and last uveitis episodes, number of uveitis episodes, follow-up time in months, recorded ocular pareses, pathological mydriasis, ptosis, presence of keratitis and corneal scarring, elevated IOP, glaucoma, cataract, posterior synechiae, iris transillumination defects, skin lesions around the eye, other ocular complications and treatment. To compensate for missing data on VA at the given time points, we evaluated whether VA values were documented before and after that time point, and we took the mean VA from those time points. We decided to only apply this if the difference in VA between those two time points was ≤ 0.2 Snellen lines, otherwise the VA value was set to missing. Additional information gathered at the present state evaluation was: presence of ocular pareses or residuals thereof (reaction of the pupil to light and eye movements), pathological mydriasis, ptosis, presence of posterior synechiae or iris transillumination defects and activity of the AU. Elevated IOP was defined as a measured IOP > 20 mmHg without pressure reducing medication. Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities. Active uveitis was defined as ≥ 0.5+ cells in the anterior chamber, inactive uveitis as < 0.5+ cells in the anterior chamber (regardless of medication use for uveitis) and remission as < 0.5+ cells in the anterior chamber without medication use for uveitis, according to the SUN Working Group criteria.[14] The date of the last visit related to the last uveitis episode was taken as the "end of follow-up", i.e. the end of follow-up for the retrospective study.

For the present state evaluation, all unilateral AU patients were invited to visit the outpatient department one additional time. The present state evaluation thus took place after the last visit related to the last uveitis episode (end of follow-up of the retrospective study). During this evaluation the pupil diameters were measured by a Colvard pupillometer (REF 0401, SN-2943), using a fixed light intensity between 420-440 lux. measured by a photometer (EG&G, model 450-1) with a photometric filter. Accommodation was controlled through distance fixation. The eyelid openings were measured using a ruler with mm division. A ptosis or anisocoria were defined as more than one mm difference between fellow eyes. In the presence of (sectorial) iris transillumination defects, the smallest measured pupil diameter was taken, thus excluding the area of iris transillumination from the measurement, minimizing the influence of the atrophic

area on the measurement.

Data were statistically analyzed using SPSS Statistics 20.0.0.1 and MedCalc 13.2.2.0. For the comparison of proportions we used the chi-square test or the Fisher's exact test. For the comparison of continuous variables of two groups, we used the independent-samples t-test (if data were normally distributed) or the Mann-Whitney U test (if data were not normally distributed). For analyzing, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent. Ocular complications were expressed as percentages during follow-up and as rate/eye-years (EY) to correct for variable follow-up between groups. Rates/EY were calculated by dividing the number of events (e.g., eyes with glaucoma) by the sum of the follow-up time of all included eyes. A multivariate Cox regression model was created to analyze risk factors for cataract extraction and glaucoma intervention. There was a significant difference when $p<0.05$.

RESULTS

Herpetic AU (retrospective study)

Data of 62 herpetic AU patients were available for analysis. Forty-five patients had a presumably HSV- and 17 patients a presumably VZV-associated uveitis. Most diagnostic criteria did not differ between both groups, except for keratitis, which was more often seen in HSV AU, and skin lesions, which were only observed in VZV patients (Table 1).

Table 2 shows the clinical characteristics of the herpetic AU patients. Differences were that VZV AU patients had a shorter duration of follow-up with more single uveitis episodes without recurrence and a higher age at uveitis onset. HSV and VZV AU were comparable with regard to gender, laterality, total uveitis episodes and the use of antiviral medication.

All patients were treated with ocular corticosteroids at the time of active uveitis, with a maximum of 16 drops a day. In case of a persistent and severe uveitis, additional oral corticosteroids or peri-ocular corticosteroid injections were given. 4/62 (6%) patients used short-term oral corticosteroids and to 3/62 (5%) patients a peri-ocular corticosteroid injection was given. 57/62 (92%) patients received additional anti-viral medication. Table 2 shows when systemic anti-viral medication was started in relation to the number of uveitis episodes. In 36/62 (58%) of herpetic patients anti-viral medication was started during the first and in 9/62 (15%) during the second uveitis episode. Keratitis was seen in 28/36 (78%) patients who started anti-viral medication during the first uveitis episode and in 11/26 (42%) patients who started anti-viral medication later on or not at all ($p=0.004$).

Table 1: Diagnostic criteria herpetic AU patients

	HSV (n=45)	VZV (n=17)	Total (n=62)	p value[c] HSV vs VZV
AU	45 (100%)	17 (100%)	62 (100%)	-
Keratitis	32 (71%)	7 (41%)	39 (63%)	**0.030**
High intraocular pressure[a]	34 (76%)	10 (59%)	44 (71%)	0.222
Iris transillumination defects	20 (44%)	4 (24%)	24 (39%)	0.131
Positive anterior chamber tap[b]	10 (22%)	3 (18%)	13 (21%)	1.000
Skin lesions (HZO)	0 (0%)	13 (76%)	13 (21%)	**<0.001**

[a]High intraocular pressure at the start of a uveitis episode. [b]Positive anterior chamber tap on local antibody production or the presence of virus DNA by PCR. [c]There was a significant difference when p<0.05. Abbreviations: AU (anterior uveitis), PCR (polymerase chain reaction), HZO (herpes zoster ophthalmicus), HSV (herpes simplex virus), VZV (varicella zoster virus)

Table 2: Clinical characteristics herpetic AU patients for the retrospective study

	HSV (n=45)	VZV (n=17)	Total (n=62)	p value[c] HSV vs VZV
Gender (% female)	16 (36%)	5 (29%)	21 (34%)	0.648
Age at first episode (yrs)[a]	47 ± 20 (5-78)	58 ± 19 (24-85)	50 ± 20 (5-85)	**0.039**
Unilateral / bilateral	45 (100%) / 0 (0%)	17 (100%) / 0 (0%)	62 (100%) / 0 (0%)	1.000
Follow-up (yrs)[b]	4.0 (0.02-41.3)	0.2 (0.1-27.7)	2.5 (0.01-41.3)	**0.010**
Total uveitis episodes[b]	3.0 (1-27)	1.0 (1-10)	2.0 (1-27)	0.102
Single episode, no recurrence (n (%))	10 (22%)	10 (59%)	20 (32%)	**0.006**
Use of systemic antiviral medication	41 (91%)	16 (94%)	57 (92%)	1.000
- Start uveitis episode 1	*23 (51%)*	*13 (77%)*	*36 (58%)*	-
- Start uveitis episode 2	*8 (18%)*	*1 (6%)*	*9 (15%)*	-
- Start after uveitis episode 2	*10 (22%)*	*2 (12%)*	*12 (19%)*	-

[a]Mean with standard deviation and range. [b]Median with range. [c]There was a significant difference when p<0.05. Abbreviations: AU (anterior uveitis), HSV (herpes simplex virus), VZV (varicella zoster virus)

Table 3 shows the ocular complications in HSV and VZV AU. The most common finding in herpetic AU already present at presentation was keratitis in 39/62 (63%) of patients (shown in Tables 1 and 3 because keratitis at presentation can be complicated by corneal scarring during follow-up). Complications that developed during follow up were cataract in 25/62 (40%), posterior synechiae in 19/62 (31%) and glaucoma in 14/62 (23%) patients. An elevated IOP at any time was seen in 44/62 (71%) patients of the herpetic group (shown in Table 1, because in the herpetic group this was an inclusion criterion). Incidence rates/EY of ocular complications are also given in Table 3. The incidence rate/EY of any ocular complication was higher in VZV AU patients compared to HSV AU patients, 0.281/EY versus 0.117/EY , p=0.003. The incidence rates/EY of single ocular complications did not differ between HSV and VZV AU. Twelve herpetic AU patients had had a glaucoma intervention during follow-up.

Table 3: Development of ocular complications in herpetic AU during follow-up (retrospective study)

	HSV (n=45)	VZV (n=17)	Total (n=62)	p value HSV vs VZV	Rate/EY[c] HSV	95% CI	Rate/EY[c] VZV	95% CI	Rate/EY[c] Total	95% CI	P value[d] Rate/EY HSV vs VZV
Any ocular complication	43 (96%)	15 (88%)	58 (94%)	0.300	0.117	0.08 – 0.16	0.281	0.16 – 0.46	0.140	0.10 – 0.18	0.003
Keratitis	32 (71%)	7 (41%)	39 (63%)	0.030	0.087	0.06 – 0.12	0.131	0.05 – 0.27	0.093	0.07 – 0.13	0.323
- Without residual	10 (22%)	3 (18%)	13 (21%)	1.000	0.027	0.01 – 0.05	0.056	0.01 – 0.16	0.031	0.02 – 0.05	0.260
- With mild peripheral scarring	6 (13%)	2 (12%)	8 (13%)	1.000	0.016	0.01 – 0.04	0.038	0.004 – 0.14	0.019	0.01 – 0.04	0.295
- With severe central scarring	16 (36%)	2 (12%)	18 (29%)	0.071	0.044	0.02 – 0.07	0.038	0.005 – 0.14	0.043	0.03 – 0.07	0.841
Cataract	19 (42%)	6 (35%)	25 (40%)	0.620	0.052	0.03 – 0.08	0.113	0.04 – 0.25	0.059	0.04 – 0.09	0.089
- Cataract extraction needed[a]	12 (27%)	2 (12%)	14 (23%)	0.313	0.033	0.02 – 0.06	0.038	0.005 – 0.14	0.033	0.02 – 0.06	0.857
Posterior synechiae	14 (31%)	5 (29%)	19 (31%)	0.897	0.038	0.02 – 0.06	0.094	0.03 – 0.22	0.045	0.03 – 0.07	0.074
Glaucoma	10 (22%)	4 (24%)	14 (23%)	1.000	0.027	0.01 – 0.05	0.075	0.02 – 0.19	0.033	0.02 – 0.06	0.070
IOP reducing intervention needed	10 (22%)	2 (12%)	12 (19%)	0.484	0.027	0.01 – 0.05	0.038	0.005 – 0.14	0.029	0.02 – 0.05	0.678
CME	1 (2%)	0 (0%)	1 (2%)	1.000	0.003	<0.001 – 0.02	0.000	0.00 – 0.07	0.002	<0.001 – 0.01	0.703
Other ocular complications[b]	5 (11%)	1 (6%)	6 (10%)	0.662	0.014	0.004 – 0.03	0.019	<0.001 – 0.10	0.014	0.01 – 0.03	0.769

[a]Cataract extraction performed before end of follow-up AU. [b]Other ocular complications included: pigment dispersion (n=2), decompensated cornea (n=1), scleritis (n=1), retinal angiomatous proliferation (n=1) in the HSV group and retinal detachment (n=1) in the VZV group. [c]Rate is the number of events in the eyes at risk for the event divided by total follow-up time per eye. It is calculated by dividing the number of events (e.g., eyes with glaucoma) by the sum of the follow-up time of all included eyes (typically expressed as eye-years (EY)). [d]There was a significant difference when $p<0.05$. Abbreviations: AU (anterior uveitis), CME (cystoid macular edema), HSV (herpes simplex virus), VZV (varicella zoster virus), CI (confidence interval).

In the herpetic group, 39 (63%) of patients had had keratitis in the past, 18 (29%) of whom with severe central scarring. Figure 1 shows the VA of herpetic AU patients with and without keratitis, over a period of ten years. There was no significant difference in VA between both groups in the first seven years of follow-up. At eight and nine years of follow-up, patients without keratitis scored significantly better on VA, p=0.027 and p=0.016 respectively. At ten years of follow-up there was no significant difference.

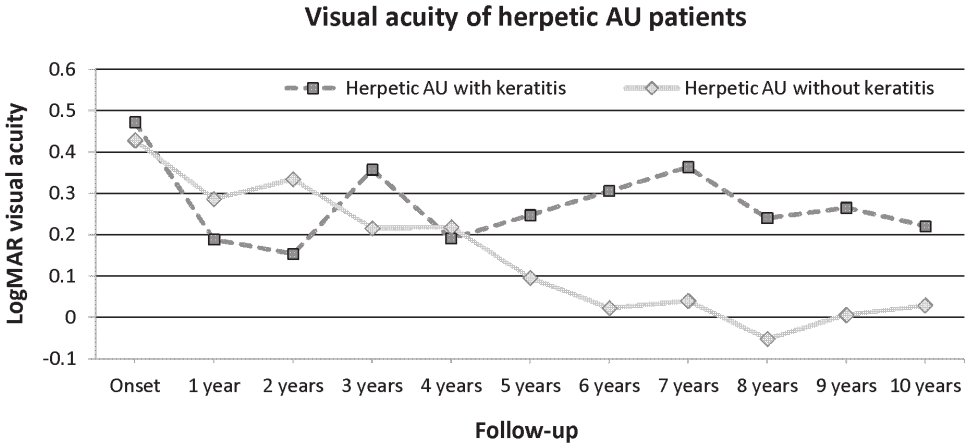

Figure 1. Visual acuity of herpetic anterior uveitis patients with and without keratitis. Visual acuity differed significantly at eight (p=0.027) and nine (p=0.016) years of follow-up. Number of AU patients with keratitis/without keratitis at consecutive intervals (onset → 10 years follow-up): n=31/21, n=24/15, n=22/15, n=19/15, n=18/14, n=18/12, n=14/11, n=15/10, n=12/8, n=11/8, n=10/7.
AU: anterior uveitis

HLA-B27 associated AU (retrospective study)

In the HLA-B27 or ankylosing spondylitis associated group, 113 patients were included, 59 (52%) with an HLA-B27 associated systemic disease (Table 4). Forty-nine (83%) of these patients had a history of ankylosing spondylitis and 10 (17%) had a history of another HLA-B27 associated systemic disease. Fifty-four (48%) HLA-B27 positive patients had no associated systemic disease. Of the patients with a history of ankylosing spondylitis, 27 (55%) patients were HLA-B27 positive and the remaining 22 (45%) patients were not tested for HLA-B27 positivity. The latter group will further be referred to as the HLA-B27 group. Table 4 summarizes the clinical characteristics.

Table 4 shows the clinical characteristics of HLA-B27 AU. Forty-six (41%) of the patients were female and the mean age at uveitis onset was 36 ± 13 years. Sixty-four (57%) patients had a bilateral disease. The median total follow-up time was 6.9 (0.02-38.7) years and patients had a median of 3.5 (1-22) AU episodes. Twenty-two (19%) patients had a single AU episode without recurrence.

Table 5 shows the ocular complications of HLA-B27 associated AU. The most common complications in HLA-B27 AU to develop during follow-up were posterior synechiae in 51/113 (45%), elevated IOP in 33/113 (29%), cataract in 25/113 (22%), CME in 10/113 (9%) and glaucoma in 4/113 (4%) patients. Incidence rates/EY of ocular complications are also given in Table 5.

Table 4: Clinical characteristics HLA-B27 AU patients for the retrospective study

	HLA-B27 (n=113)
Gender (% female)	46 (41%)
Age at first episode (yrs)[a]	36 ± 13 (10-81)
Unilateral / bilateral	49 (43%) / 64 (57%)
Follow-up (yrs)[b]	6.9 (0.02-38.7)
Total uveitis episodes[b]	3.5 (1-22)
Single episode, no recurrence (n (%))	22 (19%)
HLA-B27 tested (% of total group)[c]	87 (77%)
HLA-B27 positive (% of tested)	87 (100%)
Systemic disease	59 (52%)
- Ankylosing spondylitis (solitary)	38 (64%)
- Ankylosing spondylitis + second systemic disease[d]	11 (19%)
- Reactive arthritis (solitary)	3 (5%)
- Crohn's disease / Colitis ulcerosa (solitary)	2 (3%)
- Other[e]	5 (8%)

[a]Mean with standard deviation and range. [b]Median with range. [c] All patients that have not been tested for HLA-B27 positivity (n=26), were diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. [d] Second systemic diseases were Colitis ulcerosa (n=3), reactive arthritis (n=1), arthritis (n=1), Crohn's disease (n=2), rheumatoid arthritis (n=2) and psoriatic arthritis (n=2). [e] Other systemic diseases were spondyloathropathy (n=3), mixed connective tissue disease (n=1), reactive polyarthritis (n=1).

Table 5: Development of ocular complications in HLA-B27 AU during follow-up (retrospective study)

	HLA-B27 (n=113)	Rate/EY[c]	95 % CI
Any ocular complication	84 (74%)	0.076	0.06 – 0.09
Posterior synechiae	51 (45%)	0.046	0.03 – 0.06
Elevated IOP	33 (29%)	0.030	0.02 – 0.04
Cataract	25 (22%)	0.023	0.01 – 0.03
- Cataract extraction needed[a]	13 (12%)	0.012	0.006 – 0.02
CME	10 (9%)	0.009	0.004 – 0.02
Glaucoma	4 (4%)	0.004	<0.001 – 0.009
IOP reducing intervention needed	3 (3%)	0.003	<0.001 – 0.008
Other ocular complications[b]	7 (6%)	0.006	0.003 – 0.01

[a]Cataract extraction performed before end of follow-up AU. [b]Other ocular complications included: macular folds (n=1), episcleritis (n=2), mild scleritis (n=1), bacterial keratitis (n=1), retinal defect (n=1) and papillitis (n=1). [c]Rate is the number of events in the eyes at risk for the event divided by total follow-up time per eye. It is calculated by dividing the number of events (e.g., eyes with glaucoma) by the sum of the follow-up time of all included eyes (typically expressed as eye-years (EY)). Abbreviations: AU (anterior uveitis), IOP (intraocular pressure), CME (cystoid macular edema), CI (confidence interval).

All patients were treated with ocular corticosteroids at the time of active uveitis, with a maximum of 16 drops a day. In case of a persistent and severe uveitis, additional oral corticosteroids or peri-ocular corticosteroid injections were given. In the HLA-B27 group, 24/113 (21%) patients used short-term oral corticosteroids and to 45/113 (40%) a peri-ocular corticosteroid injection was given.

Herpetic AU (present state evaluation)

To evaluate the present state, especially possible ocular pareses and residuals thereof, 33 herpetic AU patients were included. Table 6 summarizes their clinical characteristics. Fourteen (42%) of the patients were female and the mean age at uveitis onset was 58 ± 17 years. The median total follow-up time was 4.6 (0.05-41.3) years and patients had 4.2 ± 3.2 (1-12) AU episodes. None of the patients had an active uveitis and the median remission time was 2.7 years.

Table 6: Present state evaluation herpetic group

	Total group (n=33)
Gender (%female)	14 (42%)
Present age (yrs)[a]	58 ± 17 (26-84)
Follow-up (yrs)[b]	4.6 (0.05-41.3)
Total uveitis episodes[a]	4.2 ± 3.2 (1-12)
Inactive uveitis (yrs)[b,c,d]	2.7 (0.02-10.4)
Active uveitis	0 (0%)

[a]Mean with standard deviation and range. [b]Median with range. [c]Time between the last visit related to the last uveitis episode (end of follow-up of the retrospective study) and present state evaluation. [d]Inactive uveitis is defined as <0.5+ cells in the anterior chamber, regardless of medication use for uveitis.

Table 7 gives information about ocular pareses in herpetic AU. The presence of a solitary pathological mydriasis in the uveitic eye was comparable in the retrospective and the present state evaluation, 12/62 (19%) and 6/33 (18%) respectively. There was no mentioning of posterior synechiae or the use of mydriatics at the time of the pathological mydriasis. In total, seven patients had a pathological mydriasis at the present state evaluation, which in three of them had been documented in their files (retrospective data). On the other hand, five patients in whom a pathological mydriasis was documented in their files (retrospective data), did not have a pathological mydriasis at the present state evaluation anymore. Four of fourteen (29%) patients with a pathological mydriasis retrospectively (solitary or in combination with a ptosis), had had ocular surgery in the past.

The presence of a solitary ptosis was seen in 1/62 (2%) patients in the retrospective evaluation and in 3/33 (9%) patients in the present state evaluation. The combination of a pathological mydriasis and a ptosis was scarce in the retrospective and present state evaluation. Complete oculomotor nerve pareses were not found in the retrospective evaluation, in the present state

evaluation one patient had a partial oculomotor nerve paresis. Two patients had abnormal eye movements, consistent with a n.4 paresis and a n.6 paresis, both patients had had HZO in the past.

Table 7: Ocular pareses herpetic group (retrospective versus present state evaluation)

	Retrospective (n=62)	Present state (n=33)
Mydriasis[a] (solitary)	12 (19%)	6 (18%)
Ptosis (solitary)	1 (2%)	3 (9%)
Mydriasis[a] and ptosis	2 (3%)	1 (3%)
Ptosis and abnormal eye movements	0 (0%)	1 (3%)[b]
Complete n. 3, n.4 or n. 6 paresis	2 (3%)[c]	0 (0%)

[a]Pathological mydriasis at uveitic eye, without posterior synechiae. [b]Conform oculomotor nerve paresis. [c]Abnormal eye movements in accordance with n.4 paresis and n.6 paresis.

Table 8: Present state evaluation HLA-B27 group

	Total group (n=29)
Gender (%female)	11 (38%)
Present age (yrs)[a]	51 ± 17 (17-76)
Follow-up (yrs)[b]	2.8 (0.04-27.7)
Total uveitis episodes[a]	3.5 ± 2.3 (1-10)
Inactive uveitis (yrs)[b,c,d]	1.8 (0.6-15.2)
Active uveitis	0 (0%)

[a]Mean with standard deviation and range. [b]Median with range. [c]Time between the last visit related to the last uveitis episode (end of follow-up of the retrospective study) and present state evaluation. [d]Inactive uveitis is defined as <0.5+ cells in the anterior chamber, regardless of medication use for uveitis.

Table 9: Ocular pareses HLA-B27 group (retrospective versus present state evaluation)

	Retrospective[a] (n=49)	Present state (n=29)
Mydriasis[b] (solitary)	3 (6%)	0 (0%)
Ptosis (solitary)	1 (2%)	1 (3%)
Mydriasis[b] and ptosis	1 (2%)	1 (3%)
Ptosis and abnormal eye movements	0 (0%)	0 (0%)
Complete n. 3, n.4 or n. 6 paresis	0 (0%)	0 (0%)

[a]Only unilateral AU patients included, since the fellow eye served as an internal control for ocular pareses. [b]Pathological mydriasis at uveitic eye, without posterior synechiae.

HLA-B27 / ankylosing spondylitis associated AU (present state evaluation)

We also evaluated if there were ocular pareses in HLA-B27 AU. Table 8 summarizes the clinical characteristics. Twenty-nine patients with HLA-B27 associated AU were included, ten with a history of ankylosing spondylitis, one with ankylosing spondylitis and reactive arthritis and 18 without an associated systemic disease. Eleven (38%) of the patients were female and the mean age at AU onset was 51 ± 17 years. The median total follow-up time was 2.8 (0.04-27.7) years and patients had 3.5 ± 2.3 (1-10) AU episodes. None of the patients had an active uveitis and the median remission time was 1.8 years.

Table 9 gives information about ocular pareses in HLA-B27 AU. In the retrospective evaluation, 3/49 (6%) patients had a pathological solitary mydriasis in the uveitic eye. There was no mentioning of posterior synechiae or the use of mydriatics at the time of the pathological mydriasis. In the present state evaluation, no pathological solitary mydriasis was seen. In the restrospective and the present state evaluation a solitary ptosis and the combination of a pathological mydriasis and ptosis were scarce. None of the patients with a pathological mydriasis retrospectively (solitary or in combination with a ptosis), had had ocular surgery in the past. Complete ocular pareses were not found in HLA-B27 AU.

Herpetic versus HLA-B27 AU

Table 10 shows the incidence rate/EY of ocular complications of herpetic versus HLA-B27 AU. The incidence rate/EY of any ocular complication was higher in herpetic compared to HLA-B27 AU, 0.140/EY versus 0.076/EY, p=<0.001. The incidence rates/EY of single ocular complications differed significantly for glaucoma (0.033/EY versus 0.004/EY, p<0.001) and cataract (0.059/EY versus 0.023/EY, p<0.001). The incidence rates/EY did not differ for CME and posterior synechiae.

Figure 2 shows the VA of herpetic and HLA-B27 AU patients, over a period of ten years. There was a significant difference in VA between both groups with a worse VA in the herpetic group at onset and in the first five years of follow-up (p=0.003 at onset, p=0.005 at one year, p=0.014 at two years, p=0.015 at three years, p=0.036 at four years and p= 0.029 at five years) and again at seven years of follow-up (p=0.047). At six years and between eight and ten years of follow-up the VA did not significantly differ between both groups.

A multivariate Cox regression model was created to analyze risk factors for cataract extraction and glaucoma intervention, these included type of uveitis (herpetic or HLA-B27 associated AU), age at onset of uveitis and gender. The results of the Cox regression model for cataract extraction showed that patients with a higher age have a significantly higher risk of a cataract extraction (hazard ratio (HR): 1.08; p<0.001). No significant differences were found for type of uveitis (HR: 1.80; p=0.192) and gender (HR: 0.67; p=0.342). The results of the Cox regression model for glaucoma intervention showed that patients with herpetic AU (HR: 7.51; p=0.003) and higher age (HR: 1.04; p=0.026) have a significantly higher risk of a glaucoma intervention. No significant differences were found for gender (HR: 1.46; p=0.567).

Table 10: Ocular complications HLA-B27 group compared to herpetic group

	Herpetic (n=62)	Rate/EY[a]	95 % CI	HLA-B27 (n=113)	Rate/EY[a]	95 % CI	P value[b] herpetic vs HLA-B27
Any ocular complication	58 (94%)	0.140	0.10 – 0.18	84 (74%)	0.076	0.06 – 0.09	<0.001
Glaucoma	14 (23%)	0.033	0.02 – 0.06	4 (4%)	0.004	<0.001 – 0.009	<0.001
Cataract	25 (40%)	0.059	0.04 – 0.09	25 (22%)	0.023	0.01 – 0.03	<0.001
CME	1 (2%)	0.002	<0.001 – 0.01	10 (9%)	0.009	0.004 – 0.02	0.172
Posterior synechiae	19 (31%)	0.045	0.03 – 0.07	51 (45%)	0.046	0.03 – 0.06	0.946

[a]Rate is the number of events in the eyes at risk for the event divided by total follow-up time per eye. It is calculated by dividing the number of events (e.g., eyes with glaucoma) by the sum of the follow-up time of all included eyes (typically expressed as eye-years (EY)). [b]There was a significant difference when p<0.05. Abbreviations: CME (cystoid macular edema), CI (confidence interval).

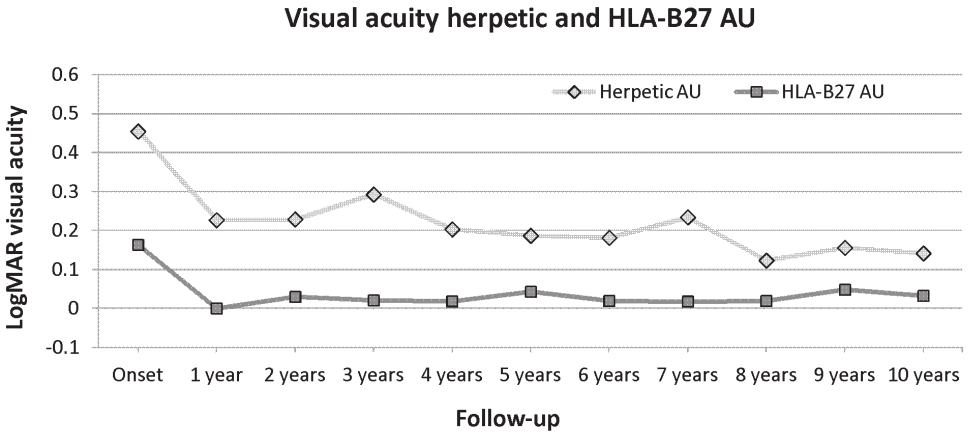

Figure 2. Visual acuity of herpetic and HLA-B27 anterior uveitis. Visual acuity differed significantly at onset (p=0.003), one (p=0.005), two (p=0.014), three (p=0.015), four (p=0.036), five (p=0.029) and seven (p=0.047) years of follow-up. Number of patients with herpetic / HLA-B27 associated AU at consecutive intervals (onset → 10 years follow-up): n=52/105, n=39/80, n=37/79, n=34/73, n=32/65, n=30/65, n=25/67, n=25/64, n=20/59, n=19/58, n=17/54. AU: anterior uveitis

DISCUSSION

In our study, we used similar definitions of clinical characteristics and complications in two groups of herpetic AU patients and in HLA-B27 associated AU patients. Using rate/EY enables us to directly compare these groups with regard to various characteristics, even if they vary in follow-up time. The results show similarities and differences between HSV and VZV AU and between herpetic and HLA-B27 associated AU. In herpetic AU, the most common clinical manifestations were elevated IOP and keratitis, and the most common complications were corneal scarring,

cataract, posterior synechiae, and glaucoma. The incidence rate of any ocular complication was higher in VZV AU patients compared to HSV AU patients, although incidence rates/EY of single ocular complications did not differ between HSV and VZV AU. Herpetic patients without keratitis scored somewhat better on VA, especially during follow-up. The most common complications in HLA-B27 AU were posterior synechiae, elevated IOP, cataract, CME and glaucoma. The incidence rate of any ocular complication was higher in herpetic AU compared to HLA-B27 associated AU , which was mainly due to higher incidence rates of glaucoma and cataract in herpetic AU. HLA-B27 associated AU patients scored better on VA at onset and during follow-up, compared to herpetic AU.

We found that HLA-B27 AU has a relatively good visual prognosis. At onset, VA is lowest, which is probably due to the active uveitis. At one year of follow-up, the mean VA is almost 20/20 and it remains so during further follow-up (until 10 years after onset). In the literature, HLA-B27 AU also has a relatively good visual prognosis. However, previous studies also described visual impairment in a substantial proportion of patients, e.g. a Snellen VA of 0.1 to 0.4 in 9 out of 59 (9%) uveitic HLA-B27 eyes [11] and in 6 out of 63 (10%) HLA-B27 AU patients, respectively.[3] These studies were also conducted at tertiary referral centers and had follow-up times of 2.9 years (median) [11] and of 4.3 years (mean) [3], respectively. In the study by Power et al. 26/291 (9%) of eyes even became legally blind.[12]

Overall, VA outcomes in herpetic AU were lower than those in HLA B27 associated AU. A similar finding in both groups was the lower VA at the onset of AU, which in both groups is probably due to the active uveitis. In herpetic AU, mean VA at one year of follow-up and onwards is better than that at onset and no significant differences in VA at onset and during the first seven years of follow-up were found between eyes with and those without keratitis. At a later stage, VA was lower in herpetic patients with keratitis as compared to those without. In addition, at ten years of follow-up, VA of herpetic AU patients without keratitis seemed to be comparable with that of HLA-B27 AU patients. Tugal-Tutkun et al. also reported that in their study Snellen VA was less (< 0.5) in 17 of 111 (15%) of patients due to corneal involvement. They also reported that patients with only iridocyclitis had no permanent visual loss. The patients in their study had a shorter duration of follow-up (median 22.4 months, range 1 - 96 months).[7]

In our study, by using the same definitions for ocular complications, VZV AU patients had a higher incidence rate of any ocular complication, compared to HSV AU patients, whereas herpetic AU patients had a higher incidence rate of any ocular complication, compared to HLA-B27 AU patients. VZV AU patients had a shorter duration of follow-up compared to HSV AU patients and herpetic AU patients had a shorter duration of follow-up, compared to HLA-B27 AU patients. This may suggest that the majority of ocular complications occur early in the course of AU.

In our study, a considerably lower percentage of eyes with glaucoma was seen in HLA-B27 as compared to herpetic AU (4% versus 23% (0.004/EY versus 0.033/EY, p<0.001)). In the literature, given rates of glaucoma vary. For herpetic uveitis, they range from 1.8 to 30%, and for HLA-B27 related AU, this varies between 0 and 20%.[6,7,12,13,15-17] Transiently elevated IOP was a common finding in herpetic AU patients (71%), however it should be mentioned that this was also one of the inclusion criteria for the herpetic group. Transiently elevated IOP was also seen in the HLA-B27 group, but less frequently (29%). In the herpetic group, 32% (23 out of 71) of patients with transiently elevated IOP developed glaucoma and in the HLA-B27 group this was 14% (4 out of 29). This suggests that transiently elevated IOP carries a higher risk of glaucoma in herpetic as compared to HLA-B27 associated AU.

The development of cataract in the course of uveitis is a well-known complication. This can be induced by the use of ocular steroids, usually resulting in posterior subcapsular cataract, by the chronic inflammation itself or by aging.[18,19] In our study, the formation of cataract was relatively high in the herpetic group as compared to the HLA-B27 group (40% versus 22% (0.059/EY versus 0.023, p<0.001)). This difference could be related to the fact that herpetic patients were older and are therefore more likely to develop age-related cataract in addition to cataract secondary to their uveitis. This is supported by our sub analyses on risk factors for cataract extraction. This analysis showed that higher age gives a higher risk of a cataract extraction. Alternatively, the virus might infect the lens, thereby resulting in cataract formation. Support to this possible mechanism is given by previous research in a mouse model, which demonstrated that inoculation of the cornea with HSV-1 may result in a secondary HSV infection in the lens leading to cataract formation.[20] Another study found evidence of possible HSV-1 involvement in congenital cataract formation in humans.[21] The latter hypothesis is not supported by our sub analysis, since the type of uveitis was not a risk factor for cataract extraction. With regard to the overall prevalence of cataract, our results are in agreement with the literature, since previous studies gave a prevalence of cataract of 20 - 32% in HSV and 12.5 - 29% in VZV patients.[6,8]

In our study, the presence of a pathological mydriasis in the uveitic eye was more common in herpetic as compared to HLA-B27 AU. In theory, this could be due to a preganglionic oculomotor nerve paresis. However, since we did not observe complete oculomotor pareses and only rarely any other ocular pareses, it is unlikely that the central oculomotor nerve is involved in this group. This is in contrast to earlier studies where ocular pareses were common in HZO patients and to a lesser extent in HSV patients.[9,10] Probably, changed therapeutic strategies, in particular the use of systemic antiviral medication early in the disease process in HZO patients, has contributed to this difference. Alternatively, a postganglionic oculomotor nerve paresis could play a role. Pathological mydriasis due to a peripheral oculomotor nerve paresis is also referred to as an Adie's tonic pupil.[22] Some case-reports found an association between VZV infection and a postganglionic oculomotor nerve paresis[23-25] or an opticopathy.[26] A study on 13 uveitis patients reports on an association between HSV ocular infection and persistent mydriasis.[27] In addition,

ocular surgery can cause a tonic pupil.[22] Another explanation for pathological mydriasis could be a degeneration of the iris sphincter muscle. At the present state evaluation, 86% of eyes with a pathological mydriasis also had sectorial iris atrophy. This indicates a shared pathogenic mechanism, which is supported by previous studies in herpetic uveitis describing an association between iris atrophy and unspecified ocular pareses or a tonic pupil.[28,29]

Ptosis, with a similar prevalence in both groups, might be related to the therapy of the uveitis rather than its cause. In the literature, numerous possible triggers for the development of ptosis have been given, including nonspecific irritation due to the inflammation, the chronic use of eye drops, peri-ocular or intravitreal injections with corticosteroids, and ocular surgery.[30,31]

Our study is mainly retrospective and has all the shortcomings related to this. Not all patients included in the retrospective study could be included in the present state evaluation. This made it impossible to compare the ophthalmic findings for each individual patient. Our patients were seen at a tertiary referral center and therefore this population may not represent the general uveitis population. Finally, most patients were diagnosed by their clinical presentation. It would be interesting to try to tie the ocular complications to the disease process or the side effects of the uveitis treatment (e.g. steroid use). However, since therapy and the disease process are entwined, this cannot reliably be done in a retrospective study. A prospective study design might be more suitable for this purpose.

In conclusion, this study provides information on the course of VA over a long period of time and on the incidence rates/EY of ocular complications in two large uveitis entities. The most prominent finding in this study is that of a worse visual prognosis in herpetic versus HLA-B27 associated AU, which is probably related to the higher prevalence of corneal scarring and glaucoma in the former. In addition, herpetic AU patients have more ocular complications overall. We provide information that may be helpful in developing individualized entity-related counseling strategies.

ACKNOWLEDGMENTS

None

REFERENCES

1. Huang JJ, Gaudio PA. (2010) Ocular inflammatory disease and uveitis manual: diagnosis and treatment. Philadelphia, Wolters Kluwer, Lippincott Williams & Wilkins, pp. 41-60.
2. Riordan – Eva P, Emmett T, Cunningham Jr. (2011) Vaughan & Asbury's General Ophthalmology. 18th edition, New York, The McGraw-Hill Companies. Chapter 7 (ebook).
3. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, et al. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332-336.
4. Foster CS, Vitale AT. (2002) Diagnosis and Treatment of Uveitis. 1st edition, Philadelphia, Pennsylvania, W. B. Saunders Company pp. 315-332, 581-600.
5. Nussenblatt RB, Whitcup SM. (2010) Uveitis, Fundamentals and Clinical Practice. 4th edition, St. Louis, MOSBY Elsevier. pp. 184-189, 251-263.
6. Wensing B, Relvas LM, Caspers LE, et al. Comparison of rubella virus- and herpes virus-associated anterior uveitis: clinical manifestations and visual prognosis. Ophthalmology. 2011;118:1905-1910.
7. Tugal-Tutkun I, Otük-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: a retrospective study of 111 cases. Int Ophthalmol. 2010;30:559-565.
8. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis: a clinical evaluation and comparison. Ophthalmology. 2002;109:1532-1537.
9. Marsh RJ, Dulley B, Kelly V. External ocular motor palsies in ophthalmic zoster: a review. Br J Ophthalmol. 1977;61:677-682.
10. Sekizawa T, Nakamura S, Kogure K, et al. Idiopathic third cranial nerve palsy associated with herpes simplex virus infection. Br Med J. 1987;295:813.
11. Tuncer S, Adam YS, Urgancioglu M, et al. Clinical features and outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis in a Turkish patient population. Ocul Immunol Inflamm. 2005;13:367-373.
12. Power WJ, Rodriguez A, Pedroza-Seres M, et al. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998;105:1646-1651.
13. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. Am J Ophthalmol. 1996;121:47-56.
14. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
15. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 2005;50:364-388.
16. Takahashi T, Ohtani S, Miyata K, et al. A clinical evaluation of uveitis-associated secondary glaucoma. Jpn J Ophthalmol. 2002;46:556-562.
17. Rothova A, Buitenhuis HJ, Christiaans BJ, et al. Acute anterior uveitis (AAU) and HLA-B27. Br J Rheumatol. 1983;22:144-145.
18. Urban RC Jr, Cotlier E. Corticosteroid-induced cataracts. Surv Ophthalmol. 1986;31:102-110.
19. Jancevski M, Foster CS. Cataracts and uveitis. Discov Med. 2010;9:51-54.
20. Mitchell WJ, Martin JR. Herpes simplex virus type 1 replicates in the lens and induces cataracts in mice. Lab Invest. 1992;66:32-38.
21. Raghu H, Subhan S, Jose RJ, et al. Herpes simplex virus-1-associated congenital cataract. Am J Ophthalmol. 2004;138:313-314.
22. Kawasaki A. Physiology, assessment, and disorders of the pupil. Curr Opin Ophthalmol. 1999;10:394-400.
23. Fernández de Castro LE, Sarraf OA, Hawthorne KM, et al. Ocular manifestations after primary varicella infection. Cornea. 2006;25:866-867.
24. Orssaud C, Roche O, El Dirani H, et al. Delayed internal ophthalmoplegia and amblyopia following chickenpox. Eur J Pediatr. 2006;165:728-729.
25. Dubois HF, van Bijsterveld OP. Internal ophthalmoparesis: an uncommon complication of varicella, a common disease. Ophthalmologica. 1977;175:263-268.
26. Stergiou PK, Konstantinou IM, Karagianni TN, et al. Optic neuritis caused by varicella infection in an immunocompetent child. Pediatr Neurol. 2007;37:138-139.
27. Goldstein DA, Mis AA, Oh FS, et al. Persistent pupillary dilation in herpes simplex uveitis. Can J Ophthalmol. 2009;44:314-316.
28. Marsh RJ, Easty DL, Jones BR. Iritis and iris atrophy in herpes zoster ophthalmicus. Am J Ophthalmol. 1974;78:255-261.
29. Kardon RH, Corbett JJ, Thompson HS. Segmental denervation and reinnervation of the iris sphincter as shown by infrared videographic transillumination. Ophthalmology. 1998;105:313-321.
30. Finsterer J. Ptosis: Causes, Presentation, and Management. Aesth Plast Surg. 2003;27:193–204.
31. Viola F, Morescalchi F, Ratiglia R, et al. Ptosis following an intravitreal injection of triamcinolone acetonide. Eye. 2007;21:421-423.

3

Risk factors for secondary glaucoma in herpetic anterior uveitis

Lisette Hoeksema, Nomdo M Jansonius & Leonoor I Los

Am J Ophthalmol. 2017; 181: 55-60

ABSTRACT

Purpose: To determine the incidence of elevated intraocular pressure (IOP) and secondary glaucoma in herpetic anterior uveitis (AU), due to either herpes simplex or varicella zoster virus, by using the Standardization of Uveitis Nomenclature (SUN) criteria, and to identify risk factors for the development of glaucoma.

Design: Retrospective, observational cohort study.

Methods: Patients with herpetic AU presenting themselves between 2001 and 2013 at the ophthalmology department of the University Medical Center Groningen were included. Main outcome measures were the incidence of elevated IOP and glaucoma and risk factors for the development of glaucoma.

Results: Seventy-three herpetic AU patients were included. Ocular complications most commonly seen during follow-up for uveitis were elevated IOP (75%), keratitis (59%), dry eyes (34%), posterior synechiae (34%), cataract (32%), and glaucoma (15%). Glaucoma patients, in comparison to non-glaucoma patients, had a higher number of IOP peaks during their follow-up for uveitis ($p<0.001$). The majority of patients with elevated IOP (91%) had this already at the start of the uveitis. Nineteen percent of the patients needed glaucoma surgery.

Conclusions: Using the SUN criteria, our study confirmed that elevated IOP and secondary glaucoma are major complications in herpetic AU. If an elevated IOP occurred, it was usually already present at the start of a uveitis episode. A risk factor for the development of glaucoma was the number of endured IOP peaks. Future studies are needed to evaluate whether early and prolonged use of antiviral and IOP-lowering medication may prevent glaucoma.

INTRODUCTION

Elevated intraocular pressure (IOP) and secondary glaucoma (IOP-related damage to the optic nerve head and accompanying visual field loss) are major ocular complications in uveitis. Reported incidences of elevated IOP and glaucoma in uveitis vary widely between as well as within the different uveitis entities. In herpetic anterior uveitis (AU), reported incidences of elevated IOP vary from 47 to 90%,[1-3] whereas reported incidences of secondary glaucoma vary between 2 and 54%.[1,2,4-6]. Possible explanations for this include non-uniform definitions and variable follow-up times.

Variability in definitions is a general problem in uveitis studies. Therefore, the Standardization of Uveitis Nomenclature (SUN) working group has defined criteria for uveitis classification and follow up, including uniform definitions of elevated IOP and glaucoma.[7]

The main objective of this study is to determine the incidence of elevated IOP and secondary glaucoma in herpetic AU, due to either herpes simplex virus (HSV) or varicella zoster virus (VZV), by using the SUN criteria. The second objective is to identify risk factors for the development of glaucoma. Identifying these risk factors can help to determine how therapeutic modalities can prevent glaucoma in this patient group.

METHODS

Ethics Statement

The Medical Ethical Committee of the University Medical Center of Groningen approved the conduction of this study.

Patients

The patients included in this study were selected from an existing database, containing all uveitis patients as of 2001 until 2013 who had been treated or are currently being treated for uveitis at the ophthalmology department of the University Medical Center Groningen (a tertiary referral center). We included patients with herpetic AU, due to HSV or VZV. At the time of inclusion, all patients were 18 years or older. In the absence of specific SUN criteria for herpetic AU, the diagnosis was made by clinical presentation (keratitis - dendritic herpes branch - followed by AU, elevated intraocular pressure (IOP) at presentation, iris sector atrophy developing over time and/or clear facial varicella zoster infection (ophthalmic branch of fifth cranial nerve) with subsequent kerato-uveitis or a positive anterior chamber tap for local antibody production or the presence of virus DNA by PCR). Facial skin lesions were considered as a strong indication of VZV-related uveitis. Keratitis can be associated with both HSV and VZV infection, but larger herpetic corneal branches were considered indicative of HSV. Because most patients were diagnosed by their clinical presentation, they were classified as "presumable" HSV or VZV AU.

Patients with multiple causes of anterior uveitis including a possibly herpetic uveitis and patients who had an elevated IOP or glaucoma before the onset of the uveitis were excluded.

Definitions

Active uveitis was defined as ≥ 0.5+ cells in the anterior chamber, inactive uveitis as < 0.5+ cells in the anterior chamber (regardless of medication use for uveitis) and remission as < 0.5+ cells in the anterior chamber without medication use for uveitis.[7] Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities and with or without elevated IOP.[7] An IOP peak was defined as an IOP > 21 mmHg, before the start of IOP-lowering medication;[7] in case of multiple measurements the highest IOP was recorded. The following definitions of IOP variables which were not defined by the SUN working group were added: Elevated IOP at the beginning of a uveitis episode was defined as an IOP > 21 mmHg in the first week of a new uveitis episode and elevated IOP during a uveitis episode was defined as an IOP > 21 mmHg after the first week of a new uveitis episode. Elevated IOP during follow-up was defined as elevated IOP (> 21 mmHg) that was recorded at least once during follow-up (beginning first uveitis episode until the end of the last uveitis episode). Short-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode. Long-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode and its continued use thereafter.

Data

The following information was collected from the medical records: age at the time of first uveitis episode (further referred to as "onset"), gender, uni- or bilateral uveitis, date of first and last uveitis episode, number of uveitis episodes, follow-up time in months of active uveitis (time between the start of the first and the end of the last uveitis episode), total follow-up time in months (time between the start of the first uveitis episode and the last recorded date in the patient record), Snellen visual acuity (VA) at onset and at the end of total follow-up, the cup-to-disc ratio of the optic disc at the end of total follow-up and ocular complications that developed during follow-up for uveitis (glaucoma, elevated IOP, scleritis, keratitis, cataract, posterior capsule opacification, papillitis, cystoid macular edema, dry eyes, posterior synechiae, and other ocular complications). Anterior chamber fibrin, corneal edema, and keratic precipitates, were also recorded. If glaucoma developed in the non-uveitic eye, this was also recorded.

Known or presumed risk factors for developing open-angle glaucoma were registered, namely a low central corneal thickness, myopia, positive family history of glaucoma, African descent, and steroid use.[8-12] In case of elevated IOP, additional information was gathered, including the time point of elevated IOP in relation to the uveitis episode (at the start of an episode, during an episode, during inactive uveitis or during uveitis in remission). Also, the total number of IOP peaks (elevated IOP > 21 mmHg with normal IOP before and after), and the highest measured IOP were

recorded. In glaucoma patients, the interval between the start of the first uveitis episode and the diagnosis of glaucoma was calculated in years. Further, the medical treatment and surgical interventions with regard to elevated IOP and glaucoma were collected, such as the number of patients treated with IOP-lowering medication, type of medication and number of agents used simultaneously, duration of use of IOP-lowering medication, number and type of surgical IOP-reducing interventions, and the interval between the start of the first uveitis episode and IOP-reducing intervention in years.

Statistics

Descriptive statistics were used, such as percentages, mean ± SD (range) for normally distributed data and median (IQR; range) for non-normally distributed data. For the comparison of proportions the chi-square test or the Fisher's exact test was used, when appropriate. For the comparison of continuous variables between two groups, the independent-samples t-test (if data were normally distributed) or the Mann-Whitney U test (if not) was used. For statistical analysis, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent, and subsequently reconverted for presentation. Data were analyzed using SPSS Statistics 20.0.0.1. A p value of 0.05 or less was considered statistically significant.

RESULTS

The medical records of 73 herpetic AU patients were analyzed. The median age of onset of uveitis was 50 (range: 5 – 85) years. Fifty-four (74%) patients had a presumably HSV- and 19 (26%) patients a presumably VZV-associated AU. The median age of HSV patients was 48 (range: 5-85) years and of VZV patients 60 (range: 24-85) years, p=0.03. In 19 (26%) patients an anterior chamber tap was performed, which tested positive for local antibody production or the presence of virus DNA by PCR in 14; in 12 patients for HSV and in two for VZV. There were 28 (38%) female patients. All patients had a unilateral AU, the fellow eye was affected in none of the patients.

Table 1 shows the ocular characteristics. Patients had a median of three (range: 1 – 27) uveitis episodes. Twenty-four of 73 patients had a single uveitis episode, 14 (58%) of whom had a presumably HSV and 10 (42%) a presumably VZV-associated AU, p=0.048. Median Snellen VA was significantly better at the end of total follow-up, compared to at first uveitis presentation, 0.80 (range: FC (finger counting) to 1.26)) versus 0.67 (range: HM (hand movement) to 1.50, p=0.008). During follow-up for uveitis, the following events were noted at least once (Table 1): anterior chamber fibrin in eight (11%), corneal edema in 37 (51%), and keratic precipitates in 65 (89%) patients. Table 2 shows the ocular complications most commonly seen during follow-up for uveitis, these were elevated IOP (75%), keratitis (59%), dry eyes (34%), posterior synechiae (34%), cataract (32%), and glaucoma (15%). The majority of patients with elevated IOP (91%) had elevated IOP at the start of one or more uveitis episodes. Glaucoma developed during follow-up for uveitis

after a median interval of 3.9 (range: 0.2 – 22.7) years. None of the patients with glaucoma in the eye with uveitis developed glaucoma in their fellow eye. There was no significant difference in the incidence of glaucoma (9/54 (17%) versus 2/19 (11%), p=0.7) or elevated IOP (42/54 (78%) versus 13/19 (68%), p=0.5) between HSV and VZV patients, respectively.

Table 1: ocular characteristics of herpetic anterior uveitis patients (n (% of total) or median (min, IQR, max)), n=73

Total uveitis episodes	**3 (1, 1 – 6, 27)**
Single uveitis episode, no recurrence	24 (34%)
Follow-up (active uveitis) (yrs) [a]	2.7 (0.01, 0.1 – 9.8, 43.8)
Follow-up (total) (yrs)[b]	9.1 (0.1, 3.8 – 15.2, 44.9)
Remission time (yrs)[c]	3.3 (0.1, 1.9 – 5.3, 16.3)
LogMAR VA uveitis eye (onset uveitis)	0.17 (-0.18, 0.00 – 0.40, 2.52)
(Snellen VA onset uveitis)[d]	*(0.67 (HM, 0.40 – 1.00, 1.50))*
LogMAR VA uveitis eye (end total follow-up)	0.10 (-0.10, 0.00 – 0.22, 1.77)
(Snellen VA end total follow-up)[d]	*(0.80 (FC, 0.60 – 1.0, 1.26))*
Anterior chamber fibrin[e]	8 (11%)
Corneal edema[e]	37 (51%)
Keratic precipitates[e]	65 (89%)

[a] Time between the start of the first and the end of the last uveitis episode. [b] Time between the start of the first uveitis episode and the last recorded date in the patient record. [c] Time between the end of the last uveitis episode and the last recorded date in the patient record. [d] Difference in visual acuity at onset of uveitis and end of total follow-up was statistically significant (p=0.008). [e] At the time of active uveitis. VA: Visual Acuity, HM: hand movement, FC: finger counting

Table 2: ocular complications of herpetic anterior uveitis patients (n (% of total)), n=73

Elevated IOP	**55 (75%)**
Keratitis	43 (59%)
Dry eye[a]	25 (34%)
Posterior synechiae	25 (34%)
Cataract	23 (32%)
Glaucoma	11 (15%)
Posterior capsule opacification	7 (10%)
Cystoid macular edema	3 (4%)
Scleritis	1 (1%)
Papillitis	0 (0%)
Other	2 (3%)[b]

[a] Medically treated. [b]Retinal detachment, retinal angiomatous proliferation / macular degeneration. IOP: Intraocular Pressure

There was no significant difference in known or presumed risk factors for the development of open-angle glaucoma (corneal thickness of less than 500 µm, high myopia (< -3 dpt) and a positive family history for glaucoma) between patients with and without glaucoma. The majority of patients (97%) were Caucasian. (missing data: corneal thickness 51%, myopia 5%, family history positive for glaucoma 56%, ethnicity 53%) .

Overall, 66/73 (90%) of the patients were treated with systemic antiviral medication, 38/66 (58%) of whom started during the first uveitis episode, 11/66 (17%) started during the second uveitis episode, and 17/66 (26%) started after the second uveitis episode. In addition, 47/73 (64%) of the patients received IOP-lowering medication at least once, 33/73 (45%) of whom were treated with IOP-lowering medication solely and 14/73 (19%) needed a surgical pressure reducing intervention, consisting mainly of an implantation of a Baerveldt glaucoma drainage device (79%). The median interval between the first uveitis episode and the pressure reducing intervention was 5.4 (range: 0.01 - 25.6) years. The total follow-up time did not differ between patients with IOP-lowering medication solely and patients who needed a surgical pressure reducing intervention, 12.4 ± 11.7 (range: 0.4 – 44.6) versus 11.0 ± 7.6 (range: 2.1 – 27.2; p=0.7) years. The median number of IOP-lowering agents used simultaneously was 2 (range: 1-5); the most commonly used type was a β-blocker (44/47 (94%)). Most patients used the IOP-lowering medication for a short period of time (30/47 (64%)). All patients were treated with topical corticosteroids at the time of active uveitis, with a maximum of 16 drops a day. In case of a persistent and severe uveitis, additional oral corticosteroids (6/73, 8%) or peri-ocular corticosteroid injections (8/73, 11%) were given.

Table 3 shows the patient and ocular characteristics of patients with and without glaucoma. Glaucoma patients, in comparison to non-glaucoma patients, are more often characterized by a higher number of IOP peaks during follow-up for uveitis. Glaucoma patients were more often medically treated with IOP-lowering medication, needed more IOP-lowering agents and used these IOP-lowering agents more often for a longer period of time. Use of steroids (topical, oral or ocular injections) did not differ between the two groups. In addition, there was no significant difference in corneal edema (64 versus 48%; P=0.4), anterior chamber fibrin (27 versus 8%; P=0.08), keratic precipitates (82 versus 90%; P=1.0), keratitis (45 versus 61%; P=0.3), posterior synechiae (45 versus 32%; P=0.5), and iris transillumination (36 versus 50%; P=0.4) between patients with and without glaucoma.

Table 3: patient and ocular characteristics of patients with and without secondary glaucoma (n (% of total) or median (min, IQR, max))

	Total group	Eyes with glaucoma[a]	Eyes without glaucoma[b]	p value, glaucoma vs non-glaucoma
Clinical characteristics				
Number of eyes	73	11	62	
Gender (male/female)	45 (62%) / 28 (38%)	9 (82%) / 2 (18%)	36 (58%) / 26 (42%)	0.19
Age of onset of uveitis	50 (5, 32-64, 85)	52 (28, 39-66, 75)	50 (5, 31-64, 85)	0.54
Age at end of total follow-up	63 (25, 51-76, 90)	71 (39, 43-77, 81)	61 (25, 52-76, 90)	0.47
HSV / VZV	54 (74%) / 19 (26%)	9 (82%) / 2 (18%)	45 (73%) / 17 (27%)	0.72
Number of uveitis episodes				0.17
1	26 (36%)	1 (9%)	25 (40%)	
2 - 4	24 (33%)	6 (55%)	18 (29%)	
> 4	21 (29%)	4 (36%)	17 (27%)	
Unknown	2 (3%)	0 (0%)	2 (3%)	
Follow-up (yrs)	7.9 (0.01, 0.1 – 9.8, 43.8)	6.0 (0.8, 1.6 – 7.8, 25.6)	1.6 (0.01, 0.06 – 10.3, 43.8)	0.40
Average cup-to-disc ratio end follow-up[c]	0.3 (0.1, 0.1 – 0.5, 0.9)	0.8 (0.4, 0.7-0.8, 0.9)	0.3 (0.1, 0.1-0.4, 0.7)	<0.001
IOP				
Number of IOP peaks				<0.001
0	17 (23%)	0 (0%)	17 (27%)	
1 - 2	24 (33%)	0 (0%)	24 (39%)	
> 2	23 (32%)	7 (64%)	16 (26%)	
Unknown	9 (12%)	4 (36%)	5 (8%)	
Highest IOP measured (mmHg)	38 ± 10 (22 – 65)	46 (36, 40 – 48, 48)	35 (22, 29 – 44, 65)	0.19
Systemic antiviral medication				
Start uveitis episode 1 or 2 / start after uveitis episode 1 or 2 or no antiviral treatment	49 (67%) /24 (33%)	7 (64%) / 4 (36%)	42 (68%) / 20 (32%)	0.79
Antiglaucoma medication				
Number of patients treated with antiglaucoma medication	47 (64%)	11 (100%)	36 (58%)	0.006
Number of antiglaucoma agents used simultaneously	2 (1, 1 – 3, 5)	3 (2, 3 – 4, 5)	2 (1, 1 – 3, 4)	<0.001
Duration of treatment with antiglaucoma medication				
- Short-term use / long-term use[d]	30 (64%) / 16 (34%)	0 (0%) / 10 (91%)[e]	30 (83%) / 6 (17%)	<0.001
Surgical intervention	14 (19%)	10 (91%)	4 (7%)	<0.001

[a] Date of diagnosis of glaucoma is end of follow-up. [b] End of last uveitis episode is end of follow-up. [c] End of last uveitis episode. [d] Short-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode. Long-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode and thereafter as the uveitis was quiet. [e] One patient missing. IOP: Intraocular Pressure

DISCUSSION

Using the SUN criteria, our study confirmed that elevated IOP and secondary glaucoma are major complications in herpetic AU patients. In the majority of the patients, the elevated IOP was measured at the start of a uveitis episode. Risk factors for the development of glaucoma were the number of IOP peaks. Also, use and prolonged use of IOP-lowering medication, and the number of IOP-lowering agents used simultaneously were higher in glaucoma patients. A large proportion (19%) of the herpetic AU patients needed a surgical pressure reducing intervention.

In herpetic AU, outflow obstruction due to swelling of inflamed trabecular meshwork structures and depositioning of inflammatory cells and debris are considered to be important in the pathogenesis of increased IOP and glaucoma.[13] Another common mechanism is secondary angle closure glaucoma related to the formation of peripheral anterior synechiae. Steroid induced glaucoma is an important contributor in any type of uveitis, since the application of steroids is the mainstay of uveitis treatment. In the majority of our patients, the elevated IOP was measured at the start of a uveitis episode, which supports the mechanism of obstruction due to inflammation.

The incidence of secondary glaucoma in our study was 15% after a median follow-up of 7.9 years. This is much higher than that of primary open angle glaucoma in a normal Dutch population of 55 years and older (n=3842), where a 5-year risk of probable open angle glaucoma was found to be 1.2% and of definite open angle glaucoma 0.6%[14] The 10-year risk of primary open angle glaucoma was found to be 2.8% in the same cohort, with a mean age of 65.8 year (n=2571).[15]

The frequency of elevated IOP in herpetic AU as reported in the literature varies, which is mainly due to the variation in used definitions. In our study, following the SUN classification,[7] elevated IOP was defined as a measured IOP > 21 mmHg, resulting in an incidence of 75%. Wensing et al. reported IOP > 30 mmHg in 18/39 (46%) of HSV and in 5/10 (50%) of VZV AU eyes,[4] van der Lelij et al. an IOP > 23 mmHg in 28/31 (90%) of herpetic AU eyes,[3] Tugal-Tutkun et al. an IOP > 22 mmHg in 58/114 (51%) of herpetic AU eyes[1] and Sungur et al. a temporary rise in IOP during an active uveitis period in 36/76 (47%) of herpetic AU eyes.[2] In spite of these apparent differences, elevated IOP is generally reported in at least half of herpetic AU eyes. Since elevated IOP at the start of a uveitis episode is considered to be indicative of a herpetic cause of the uveitis, studies may over report elevated IOP due to selection bias. In other words, in case elevated IOP at the start of a uveitis episode is absent, these eyes are less likely to be diagnosed as herpetic AU.

Our incidence of secondary glaucoma (15%) is comparable to the study of Sungur et al. in herpetic (HSV and VZV) AU and of Wensing et al. in HSV AU eyes. They found secondary glaucoma in 10/76 (13%) and 7/38 (18%) of eyes, respectively.[2,4] Wensing et al. used a definition related to ours, an IOP of more than 21 mmHg and the presence of disc abnormalities, of visual field defects typical

for glaucoma, or both.[4] Sungur et al used a different definition, namely a permanent IOP rise during the remission period – irrespective of disc abnormalities and/or visual field defects.[2] Other studies differ from ours and vary among each other with regard to the reported incidences of secondary glaucoma. Tugal-Tutkun et al. reported secondary glaucoma in 2/114 (2%) of herpetic AU eyes, Miserocchi et al. in 24/44 (54%) of HSV and 9/24 (38%) of VZV uveitis eyes, Wensing et al. in 3/10 (30%) of VZV AU eyes and Takahashi et al. in 7/23 (30%) of herpetic AU eyes.[1,4-6] Takahashi et al. defined secondary glaucoma as an IOP higher than 21 mmHg at two consecutive visits and the need for IOP-lowering medication.[5] In the studies of Miserocchi et al. and Tugal-Tutkun et al. there are no specified definitions of secondary glaucoma or elevated IOP.[1,6] In the study of Miserocchi et al., it is not clear if secondary glaucoma and elevated IOP are considered to be synonymous, but this would explain the high incidence of secondary glaucoma in their study.[6]

It is well known that elevated IOP is a risk factor for the development of secondary glaucoma.[9,16] However, information on specific aspects of the elevated IOP that influence the development of secondary glaucoma is lacking. It is supposed that the level of IOP[17-19] and the reduced diurnal-to-nocturnal change of habitual IOP[20] are important factors. In our study, patients who developed secondary glaucoma had more often elevated IOP during follow-up for uveitis and endured significantly more IOP peaks than patients without glaucoma, supporting the concept that elevated IOP during follow-up for uveitis and IOP peaks may cause significant problems in the long run. It has proved to be difficult to determine what is the most harmful, more IOP peaks or elevated IOP for a long period of time, in particular because these parameters are strongly correlated, the number of IOP measurements is limited (that is, IOP is undersampled), and different statistical approaches give different outcomes.[21] However, even without knowing which IOP parameter is most important, the results indicate that in patients with recurrent uveitis, frequent IOP measurements and low-threshold treatment of elevated IOP may be beneficial – given the high incidence of secondary glaucoma. In addition, knowing that 35/73 (48%) patients needed two or more IOP-lowering agents simultaneously and 14/73 (19%) patients finally needed a surgical pressure reducing intervention, makes it important to prevent these serious complications by early treatment. Future studies are needed to evaluate whether such measures indeed reduce the incidence.

In addition to frequent IOP measurements and low-threshold treatment of elevated IOP, therapeutic modalities consisting of long-term antiviral treatment to prevent new uveitis episodes and IOP peaks may be beneficial. The optimum starting point and duration of treatment with antiviral medication should be established in future studies.

Our study is mainly retrospective and has all the shortcomings related to this. Our patients were seen at a tertiary referral center and therefore this population may not represent the general uveitis population. Furthermore, most patients were diagnosed by their clinical presentation. Our study evaluated a relatively large group of patients and it adhered to the SUN Working Group criteria, thus contributing to more uniform reporting on uveitis outcomes.

In conclusion, elevated IOP and secondary glaucoma are frequent complications of viral AU. Future studies are needed to evaluate whether early and prolonged use of antiviral and anti-glaucoma medication may prevent glaucoma. In addition, the described variability between studies regarding the definitions of elevated IOP and secondary glaucoma, and the resulting variation in reported incidences of these complications, underline the need for standardized criteria such as developed by the SUN working group.[7]

ACKNOWLEDGEMENTS

None

REFERENCES

1. Tugal-Tutkun I, Otük-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: a retrospective study of 111 cases. Int Ophthalmol. 2010;30(5):559-565.
2. Sungur GK, Hazirolan D, Yalvac IS, Ozer PA, Aslan BS, Duman S. Incidence and prognosis of ocular hypertension secondary to viral uveitis. Int Ophthalmol. 2010;30(2):191-194.
3. Van der Lelij A, Ooijman FM, Kijlstra A, Rothova A. Anterior uveitis with sectoral iris atrophy in the absence of keratitis: a distinct clinical entity among herpetic eye diseases. Ophthalmology. 2000;107(6):1164-1170.
4. Wensing B, Relvas LM, Caspers LE, et al. Comparison of rubella virus- and herpes virus-associated anterior uveitis: clinical manifestations and visual prognosis. Ophthalmology. 2011;118(10):1905-1910.
5. Takahashi T, Ohtani S, Miyata K, Miyata N, Shirato S, Mochizuki M. A clinical evaluation of uveitis-associated secondary glaucoma. Jpn J Ophthalmol. 2002;46(5):556-562.
6. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis: a clinical evaluation and comparison. Ophthalmology. 2002;109(8):1532-1537.
7. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-516.
8. Leske MC. Open-angle glaucoma -- an epidemiologic overview. Ophthalmic Epidemiol. 2007;14(4):166-172.
9. Boland MV, Quigley HA. Risk factors and open-angle glaucoma: classification and application. J Glaucoma. 2007;16(4):406-418.
10. Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology. 2011;118(10):1989-1994.
11. Marcus MW, Müskens RP, Ramdas WD, et al. Corticosteroids and open-angle glaucoma in the elderly: a population-based cohort study. Drugs Aging. 2012;29(12):963-970.
12. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):714 –720.
13. Hogan MJ, Kimura SJ, Thygeson P. Pathology of Herpes Simplex Kerato-Iritis. Am J Ophthalmol. 1964;57(4):551-564.
14. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology. 2005;112(9):1487-1493.
15. Czudowska MA, Ramdas WD, Wolfs RC, et al. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology. 2010;117(9):1705-1712.
16. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol. 1991;109(8):1090-1095.
17. Varma R, Hilton SC, Tielsch JM, Katz J, Quigley HA, Sommer A. Neural rim area declines with increased intraocular pressure in urban Americans. Arch Ophthalmol. 1995;113(8):1001-1005.
18. Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci. 2000;41(1):40-48.
19. Healey PR, Mitchell P, Smith W, Wang JJ. The influence of age and intraocular pressure on the optic cup in a normal population. J Glaucoma. 1997;6(5):274-278.
20. Liu JH, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003;44(4):1586-1590.
21. Wesselink C, Marcus MW, Jansonius NM. Risk factors for visual field progression in the groningen longitudinal glaucoma study: a comparison of different statistical approaches. J Glaucoma. 2012;21(9):579-585.

4

Unilateral versus bilateral HLA-B27 associated anterior uveitis: characteristics and visual prognosis

Lisette Hoeksema, Nomdo M Jansonius, J.M.M. Hooymans & Leonoor I Los

Submitted

ABSTRACT

Purpose: To evaluate whether ocular and patient characteristics differ between unilateral and bilateral (alternating or simultaneously affected) HLA-B27 associated anterior uveitis (AU) with or without systemic disease.

Methods: We performed an observational study on all uveitis patients (n=134) who visited the ophthalmology department of the University Medical Center Groningen between 2001 and 2014.

Results: Unilateral and bilateral HLA-B27 associated AU are comparable with regard to ocular complications, course of disease, visual acuity, and treatment. Differences are that bilateral patients are younger at the onset of the uveitis (31 versus 37 years (median), p=0.02) and more often have an associated systemic disease (46/74 (62%) versus 22/60 (37%), p=0.003).

Conclusion: Unilateral and bilateral HLA-B27 associated AU are generally comparable, which indicates that it is probably the same disease entity. Unilateral and bilateral patients both have a good prognosis with regard to visual acuity and the development of ocular complications.

INTRODUCTION

Anterior uveitis (AU) is the most common type of uveitis[1-3] and it is most commonly associated with HLA-B27 positivity.[4] Patients with HLA-B27 positivity can have an HLA-B27 associated systemic disease, such as ankylosing spondilitis, reactive arthritis, Crohn's disease, and psoriasis, but in approximately 80% there is no associated systemic disease.[5] The prevalence of HLA-B27 positivity in the general Caucasian population is approximately 6-10%;[6,7] in patients with AU this is about 50%.[8] The lifetime cumulative incidence of AU is approximately 1% in HLA-B27 positive persons, whereas the lifetime cumulative incidence of AU in the general population is about 0.4%.[9] Foster et al. described that most patients with HLA-B27 associated AU typically have a unilateral recurrent form, and that bilateral simultaneous and alternating AU are also possible.[7] Nussenblatt et al. described HLA-B27 associated AU as a typically unilateral acute uveitis.[10] Since in HLA-B27 AU patients the uveitis can be unilateral (always the same eye) or bilateral (simultaneous or alternating), it would be interesting to know if these different manifestations represent the same or different disease entities. In order to inform the patient regarding the prognosis of the disease and to monitor the disease in a personalized way, it would be valuable to find out if ocular and patient characteristics differ between unilateral and bilateral HLA-B27 AU.

The present study aims to evaluate whether ocular and patient characteristics differ between unilateral and bilateral HLA-B27 associated AU with or without systemic disease. For this purpose, we performed an observational study based on all uveitis patients who visited our department between 2001 and 2014.

METHODS

Ethics Statement

The Medical Ethical Committee of the University Medical Center of Groningen approved the conduction of this study. The study adhered to the tenets of the Declaration of Helsinki.

Patients

For this study, we included patients with HLA-B27 associated anterior uveitis with or without systemic disease. The patients were selected from an existing database, containing all uveitis patients as of 2001 until 2014 who had been treated or are currently being treated for uveitis at the ophthalmology department of the University Medical Center Groningen, which is a tertiary referral center. The retrospective data was collected from medical records and we collected prospective data of 49/135 (37%) patients for a present state evaluation. In case of alternating bilateral AU (only one eye affected at first presentation), the first affected eye was compared with the affected eye of the unilateral AU patients. In case of a simultaneous bilateral AU (both

eyes affected at first presentation), we randomly selected one eye. In addition, in alternating bilateral AU patients we compared the first affected with the second affected eye. At the time of inclusion, all patients were 18 years or older. Patients were HLA-B27 positive and/or were clinically diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. Patients with ankylosing spondylitis were diagnosed following the Assessment of Spondylo-Arthritis international Society classification criteria (ASAS criteria), therefore these patients have not always been tested for HLA-B27 positivity.[11] Patients with other forms or possible causes of uveitis or with elevated IOP and/or glaucoma before the onset of the uveitis were excluded.

Definitions

In this study, we use the guidelines for uniform reporting in uveitis as developed by the Standardization of Uveitis Nomenclature.[12] According to the SUN Working Group criteria, active uveitis was defined as ≥ 0.5+ cells in the anterior chamber, inactive uveitis as < 0.5+ cells in the anterior chamber (regardless of medication use for uveitis) and remission as < 0.5+ cells in the anterior chamber without medication use for uveitis. A quiet phase corresponds to inactive uveitis or uveitis in remission. Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities and with or without elevated IOP. Transiently elevated IOP was defined as an IOP > 21 mmHg, in our department measured with applanation tonometry, before the start of IOP-lowering medication. Dry eyes were defined as the presence of dry eye symptoms and need for artificial tears. Unilateral AU was defined as uveitis at the same eye during follow-up, not alternating between eyes. Bilateral AU means involvement of both eyes, alternating or affected simultaneously.

Data

We examined the medical records of all suitable patients. We collected information on the age at the time of first uveitis episode (further referred to as "onset"), gender, uni- or bilateral uveitis, date of first and latest uveitis episodes, number of uveitis episodes, follow-up time, Snellen visual acuity (VA) at onset, at specific time points during follow-up, and at the end of follow-up, and ocular complications that developed during follow-up (elevated IOP, glaucoma, scleritis, keratitis, cataract, posterior capsule opacification, papillitis, cystoid macular edema (CME), dry eyes, and other ocular complications). CME was diagnosed by optical coherence tomography. We documented the presence of anterior chamber fibrin, corneal edema, posterior synechiae, and keratic precipitates.

Statistics

We used descriptive statistics, i.e., percentages, mean ± SD (range) for normally distributed data and median (IQR; range) for non-normally distributed data. For the comparison of proportions we used the chi-square test or the Fisher's exact test when appropriate. For the comparison of continuous variables between two groups, we used the independent-samples t-test (if normally

distributed) or the Mann-Whitney U test (if not). For statistical analyses, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent. Data were analyzed using SPSS Statistics 20.0.0.1. A p-value of 0.05 or less was considered statistically significant.

RESULTS

The medical records of 134 patients with HLA-B27 associated AU with or without systemic disease were analyzed. Table 1 shows the patient characteristics. The median age of onset of uveitis was 34 years. There were 79 (59%) male patients. In total 101 patients were tested for HLA-B27 positivity and were positive, the remaining 33 patients were not tested, these patients were diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. Sixty-eight (51%) patients had an HLA-B27 associated systemic disease. Forty of these patients had a history of ankylosing spondylitis. Median age at the onset of the uveitis did not differ between patients with (36 years; range: 11 to 69; IQR: 25 to 42) and without (34 years; range: 10 to 81; IQR: 26 to 43) systemic disease (p=0.90). Sixty (45%) patients had a unilateral AU and 74 (55%) a bilateral AU. Of the bilateral patients, 70/74 (95%) had alternating AU and 4/74 (5%) had a simultaneously bilateral AU at onset. The age at onset of the uveitis was significantly lower (median age 31 years) in bilateral AU as compared to unilateral AU (median age 37 years; p=0.02). Bilateral AU was more frequently associated with systemic disease (n=46 (62%)) than unilateral AU (n=22 (37%); p=0.003). In addition, bilateral uveitis was more frequently associated with more than one HLA-B27 associated systemic disease (9/74 (12%) versus 1/60 (2%); p=0.02).

Table 2 shows the ocular characteristics. Patients with bilateral AU had a longer follow-up than patients with unilateral AU (8.9 versus 2.7 years; p<0.001). The median interval between uveitis presentation in the first and second affected eye in bilateral patients was 4.2 years (range: 0.2 – 26.6). The total follow-up time of the unilateral patients and the median interval between uveitis presentation in the first and second affected eye in bilateral patients did not differ significantly (2.7 versus 4.2 years, p=0.11). The visual acuity at onset, at various time points during follow-up, and at the end of follow-up did not differ between unilateral and bilateral patients (Figure 1). The incidence of anterior chamber fibrin, corneal edema, keratic precipitates, and posterior synechiae did not differ between groups.

Table 3 gives information on the ocular complications. Ocular complications most commonly seen in the total group, during the entire follow-up period, were elevated intraocular pressure (36%), dry eyes (20%), cataract (20%), and CME (8%). Elevated IOP was most frequently observed in the course of a uveitis episode or when the eye had reached remission 40/48 (83%), whereas IOP was mostly within normal range at the start of a uveitis episode. Despite the difference in follow-up time between the groups (8.9 versus 2.7 years, p<0.001), there was no significant difference in ocular complications.

Table 1: patient characteristics in unilateral versus bilateral HLA-B27 associated AU (n (% of total) or median (min, IQR, max)), n=134

	Total group	Unilateral AU	Bilateral AU	P value unilateral versus bilateral eyes
Number of patients [a]	134	60 (45%)	74 (55%)	-
Gender (male/female)	79 (59%) / 55 (41%)	34 (57%) / 26 (43%)	45 (61%) / 29 (39%)	0.63
Age at uveitis onset (yrs)	34 (10, 25 to 43, 81)	37 (11, 26 to 48, 69)	31 (10, 25 to 40, 81)	**0.021**
Alternating/simultaneously bilateral AU	-	-	70 (95%) / 4 (5%)	**-**
HLA-B27 tested (% of total group)[b]	101 (75%)	49 (82%)	52 (70%)	0.13
Systemic disease	68 (51%)	22 (37%)	46 (62%)	**0.003**
- Ankylosing spondylitis (solitary)	40 (30%)	14 (23%)	26 (35%)	0.14
- Ankylosing spondylitis + second systemic disease[c]	10 (8%)	1 (2%)	9 (12%)	**0.023**
- Reactive arthritis (solitary)	5 (4%)	0 (0%)	4 (5%)	0.38
- Crohn's disease / Colitis ulcerosa (solitary)	6 (5%)	4 (7%)	2 (3%)	0.41
- Other[d]	7 (5%)	2 (3%)	5 (7%)	0.46

[a] In patients with bilateral anterior uveitis, we included the first eye diagnosed with anterior uveitis. [b] All patients that have not been tested for HLA-B27 positivity (n=33), were diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. [c] Second systemic diseases were Colitis ulcerosa (n=3), reactive arthritis (n=1), arthritis (n=1), Crohn's disease (n=1), rheumatoid arthritis (n=2) and psoriatic arthritis (n=2). [d] Other systemic diseases were psoriatic arthritis (n=1), spondyloathropathy (n=3), mixed connective tissue disease (n=1), rheumatoid arthritis (n=1), reactive polyarthritis (n=1). AU: anterior uveitis

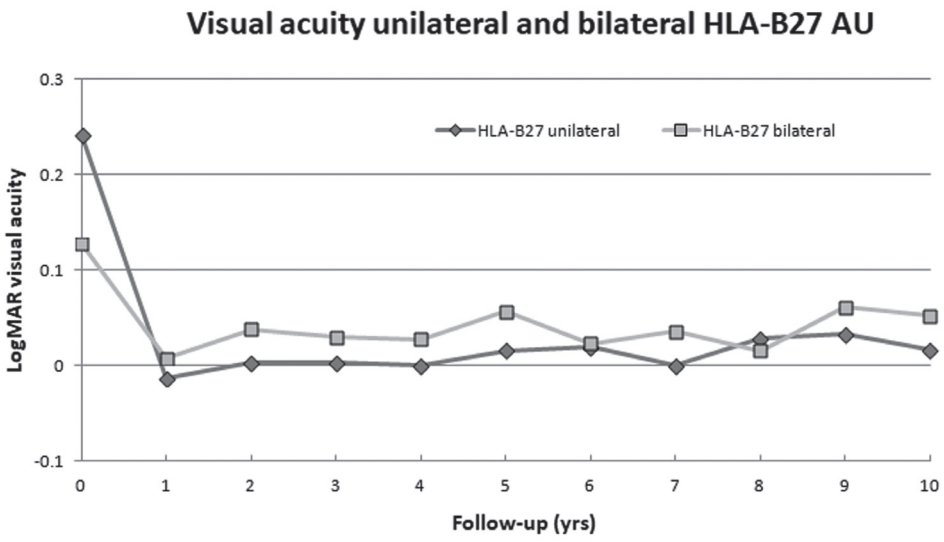

Figure 1: number of unilateral/bilateral HLA-B27 AU patients at consecutive intervals (onset → 10 years follow-up): n=59/65 (onset), n=44/53 (1 yr), n-41/53 (2 yrs), n=35/53 (3 yrs), n=27/52 (4 yrs), n=28/49 (5 yrs), n=24/51 (6 yrs), n=19/50 (7 yrs), n=15/46 (8 yrs), n=15/45 (9 yrs), n=12/46 (10 yrs). P> 0.05 at all time points. AU: anterior uveitis

Table 2: ocular characteristics in unilateral versus bilateral HLA-B27 associated AU (n (% of total) or median (min, IQR, max)), n=134

	Total eyes	Unilateral AU	Bilateral AU	P value unilateral versus bilateral eyes
Number of patients[a]	134	60	74	-
Total uveitis episodes	3 (1, 2 to 6, 22)	3 (1, 1 to 5, 22)	4 (1, 2 to 7, 22)	**0.025**
Single uveitis episode, no recurrence	25 (19%)	13 (22%)	12 (16%)	0.49
Follow-up (yrs)[b]	6.3 (0.02, 1.2 to 15.0, 38.7)	2.7 (0.02, 0.2 to 9.3, 27.1)	8.9 (0.02, 2,4 to 19.5, 38.7)	**<0.001**
LogMAR VA uveitis eye (onset uveitis)	0.05 (-0.15, 0.0 to 0.15, 2.5)	0.1 (-0.1, 0.0 to 0.3, 2.5)	0.0 (-0.15, 0.0 to 0.1, 2.5)	0.079
(Snellen VA onset uveitis)	*0.9 (HM, 0.7 to 1,0, 1.4)*	*0.8 (HM, 0.5 to 1.0, 1.26)*	*1.0 (HM, 0.8 to 1.0, 1.4)*	-
LogMAR VA uveitis eye (end follow-up)	0.0 (-0.3, -0.08 to 0.06, 0.8)	0.0 (-0.3, -0.08 to 0.1, 0.3)	0.0 (-0.20, -0.08 to 0.05, 0.8)	0.83
(Snellen VA end follow-up)	*1.0 (0.16, 0.9 to 1.2, 2.0)*	*1.0 (0.5, 0.8 to 1.2 – 2.0)*	*1.0 (0.16, 0.9 to 1.2, 1,6)*	-
Anterior chamber fibrin[c]	78 (58%)	38 (63%)	40 (54%)	0.37
Corneal edema[c]	34 (25%)	17 (28%)	17 (23%)	0.54
Keratic precipitates[c]	93 (69%)	43 (72%)	50 (68%)	0.69
Posterior synechiae	76 (57%)	35 (58%)	41 (55%)	0.80

[a] In patients with bilateral anterior uveitis, we included the first eye diagnosed with anterior uveitis. [b] Time between uveitis onset and end of last uveitis episode. [c] At the time of active uveitis. VA: Visual Acuity, HM: hand movement. AU: anterior uveitis

All patients were treated with topical corticosteroids at the time of active uveitis, with a maximum of 16 drops a day. In case of a persistent and severe uveitis, additional oral corticosteroids (34/134, 25%) or peri-ocular corticosteroid injections (57/134, 43%) were given. IOP-lowering medication was used in 34/134 (25%) of patients. Most patients used one (12/34, 35%) or two (12/34, 35%) anti-glaucoma agents simultaneously. A surgical pressure reducing intervention was performed in 5/134 (4%) of patients. Treatment of uveitis, elevated IOP, and glaucoma did not differ between unilateral and bilateral patients.

Table 4 shows the difference between the first and second affected eye in bilateral patients. The follow-up time of the first affected eye was 9.0 (range: 0.02 to 38.7, IQR: 2.6 to 19.9) versus 6.1 years (range: 0.01 to 31.1, IQR: 0.09 to 12.4) of the second effected eye (p=0.02). The number of uveitis episodes and visual acuity at presentation and at the end of follow-up did not differ between the first and second affected eye. Anterior chamber fibrin was more frequently observed in the first affected eye (56% versus 31%, p=0.004) and posterior synechiae seemed to be more frequent in the first eye (54% versus 40%) as well, but this difference did not reach significance (P=0.06). No further differences in ocular complications between first and second affected eyes were observed.

Table 3: ocular complications in unilateral versus bilateral HLA-B27 associated AU (n (% of total))

	Total eyes	Unilateral AU	Bilateral AU	P value unilateral vs bilateral uveitis
Number of patients[a]	134	60	74	-
Elevated IOP	48 (36%)	25 (42%)	23 (31%)	0.20
Dry eyes[b]	27 (20%)	15 (25%)	12 (16%)	0.21
Cataract	27 (20%)	9 (15%)	18 (24%)	0.30
CME	10 (8%)	3 (5%)	7 (10%)	0.51
Scleritis	5 (4%)	4 (7%)	1 (1%)	0.17
Posterior capsule opacification	6 (5%)	1 (2%)	5 (7%)	0.22
Glaucoma	5 (4%)	2 (3%)	3 (4%)	1.00
Papillitis	4 (3%)	3 (5%)	1 (1%)	0.33
Other	8 (6%)[c]	5 (8%)	3 (4%)	0.47

[a] In patients with bilateral anterior uveitis, we included the first eye diagnosed with anterior uveitis. [b] Medically treated. [c] Retinal defect (n=2), macular folds (n=1), bacterial keratitis (n=1), conjunctival concrements (n=1), corneal ulcer (n=1), Salzmann's Nodular Degeneration (n=1), vitreous floaters, vitrectomy required (n=1). IOP: Intraocular pressure, CME: Cystoid macular edema. AU: anterior uveitis

Table 4: first affected versus second affected eye in bilateral patients (n (% of total) or median (min, IQR, max)), n=70a

	First affected eye	Second affected eye	P value
Follow-up (yrs)[b]	9.0 (0.02, 2.6 to 19.9, 38.7)	6.1 (0.01, 0.09 to 12.4, 31.1)	0.021
Total uveitis episodes	4 (1, 2 to 7, 22)	3 (1, 1 to 7, 18)	0.37
Visual acuity at presentation (Logmar)	0.0 (-0.15, 0.0 to 0.1, 2.52)	0.0 (-0.2, -0.06 to 0.1, 1.0)	0.24
Visual acuity at presentation (Snellen)	1.0 (HM, 0.8 to 1.0, 1.4)	1.0 (0.1, 0.8 to 1.2, 1.6)	-
Visual acuity end follow-up (Logmar)	0.0 (-0.2, -0.08 to 0.05, 0.8)	0.0 (-0.2, -0.08 to 0.08, 0.9)	0.56
Visual acuity end follow-up (Snellen)	1.0 (0.16, 0.9 to 1.2, 1.6)	1.0 (0.13, 0.83 to 1.2, 1.6)	-
Anterior chamber fibrin	39 (56%)	22 (31%)	0.004
Corneal edema	16 (23%)	10 (14%)	0.19
Keratic precipitates	47 (67%)	40 (57%)	0.18
Posterior synechiae	38 (54%)	28 (40%)	0.06
Ocular complications			
- Elevated IOP	21 (30%)	20 (29%)	0.85
- Dry eyes	12 (17%)	12 (17%)	1.00
- Cataract	17 (24%)	15 (21%)	0.68
- CME	4 (6%)	9 (13%)	0.15
- Scleritis	1 (1%)	0 (0%)	1.00
- Posterior capsule opacification	5 (7%)	3 (4%)	1.72
- Glaucoma	2 (3%)	0 (0%)	0.50
- Papillitis	1 (1%)	4 (6%)	0.37

[a] patients in whom both eyes were simultaneously affected were excluded [b] Time between the start of the first uveitis episode and the end of the last uveitis episode. IOP: Intraocular Pressure, CME: Cystoid macular edema

DISCUSSION

HLA-B27 anterior uveitis is more frequently seen in men, it is mainly bilaterally alternating, and more than half of the patients have signs of a severe inflammation, such as anterior chamber fibrin and posterior synechiae. Unilateral and bilateral (alternating or simultaneously affected) HLA-B27 associated AU are generally comparable with regard to ocular complications, course of the disease, visual acuity, and treatment. Differences are that bilateral patients are younger at the onset of the uveitis and more often have an associated systemic disease.

In the total group, patients age at onset of the uveitis (median 34 years) was comparable with the literature, where the mean age range is given as 35 to 40 years.[13-20] In our study, bilateral patients were younger than unilateral patients (31 versus 37 years). As far as we know, there is no information available in the literature on differences in age at onset between unilateral and bilateral patients. Some studies compared patients with and without systemic disease. Park et al. found a mean age at uveitis onset of 32 years in patients with a systemic disease and of 39 years in those without a systemic disease (P=0.02).[21] On the other hand, Power et al. found a mean age of 36 years in patients with a systemic disease and of 34 years in those without a systemic disease (NS).[22] In our study, age at the onset of the uveitis did not differ between patients with and without systemic disease. Age at uveitis onset, therefore, seems not to predict the likelihood of having a related systemic disease.

Patients with bilateral uveitis, either simultaneous or alternating, more often had an associated systemic disease as compared to patients with unilateral uveitis (62% versus 37%, p=0.003). In addition, bilateral AU was more often associated with more than one HLA-B27 associated systemic disease. In the literature, this difference is less clear. Park et al. found bilateral uveitis in 62% of patients with a systemic disease versus 58% of patients without a systemic disease. This difference was not significant.[21] Power et al. found a bilateral AU in 54/94 (57%) of patients with a systemic disease and in 46/97 (47%)of patients without a systemic disease (P=0.22).[22] The possible association between bilateral uveitis and the presence of a systemic disease and a younger age at onset could point towards an increased activity of the immune system in these patients. The chance of detecting bilateral uveitis and systemic disease is probably related to the length of the follow-up time. In our study, the median follow-up time was 6.3 years, in the study by Park et al. 3.0 years and in the study by Power et al. 1.2 (without systemic disease) and 1.6 years (with systemic disease).

Since our patients with bilateral HLA-B27 associated AU had a significantly longer follow-up time compared to unilateral patients, we expected to find more ocular complications in the bilateral group. However, we did not find any difference between the two groups. A possible explanation for this counterintuitive finding is that most of the ocular complications occur early in the course of the uveitis. The reason for this could be that most patients will have a delay in

visiting an ophthalmologist the first time they have an active uveitis. This is confirmed by the finding in alternating bilateral patients that the first affected eye showed signs of a more severe inflammation, especially anterior chamber fibrin. Fortunately, visual acuity at the end of follow-up did not differ between the first and second affected eye.

The most frequently observed ocular complication in both groups was elevated IOP, 25/60 (42%) in unilateral patients and 23/74 (31%) in bilateral patients. In the literature, the incidence of elevated IOP in HLA-B27 positive patients with anterior uveitis ranged from 1.7 to 27.3%.[15-17,19,21,23] A small percentage of our patients developed glaucoma, 2/60 (3%) in unilateral patients and 3/74 (4%) in the bilateral group. In the literature, the incidence of secondary glaucoma ranged from 0 to 16.4%.[13,15-17,21,22,24] The frequency of elevated IOP and secondary glaucoma as reported in the literature show a wide range. A possible explanation for this variability is that most studies do not give a clear definition of elevated IOP and secondary glaucoma, or these complications are considered to be synonymous. In our study we used the SUN classifications for elevated IOP and glaucoma. Despite a relatively high percentage of patients with elevated IOP in our study, a relatively low percentage of patients developed glaucoma. A possible explanation for this can be that a short period of elevated IOP causes minimal damage and when detected is well treatable. This illustrates that AU patients do not necessarily have to become visually impaired by glaucoma. On the contrary, patients with HLA-B27 associated panuveitis, seem to have an increased risk of developing secondary glaucoma and visual loss.[20] Loh et al. found that corticosteroid-sparing therapy, corticosteroid injections and chronic disease were predictors of developing visual loss in HLA-B27 associated uveitis.[25] These observations would be consistent with a higher risk of loss of visual function in case of more extensive and more severe uveitis.

The treatment of the uveitis, especially additional oral corticosteroids and peri-ocular corticosteroid injections, did not differ between unilateral and bilateral patients. Also, the inflammatory characteristics (anterior chamber fibrin, corneal edema, keratic precipitates and posterior synechiae) were the same in the two groups. Both findings indicate that the severity of the uveitis is comparable in both groups, and that unilateral or bilateral involvement of the eyes has no predictive value here.

HLA-B27 positive anterior uveitis is often described as a unilateral recurrent uveitis.[7,10] In our study 55% (74/134) had a bilateral, mainly alternating, disease. In the literature, the prevalence of bilateral (alternating) disease varies from 27 to 52%,[13,15,17,18,22,25,26] showing that a significant percentage of patients have involvement of both eyes. Given the high percentages of patients with an associated systemic disease, the involvement of both eyes, somewhere in the disease, seems logical. In our study, the median interval between uveitis in the first and second eye was 4.2 years. Additionally, the total follow up of the unilateral patients was 2.7 years. Therefore, it could well be that the second eye of seemingly unilateral patients will get involved in the future and that the number of bilateral patients will increase.

A limitation of our study is that it is mainly retrospective and has all the shortcomings related to this. Further, our patients were seen at the only tertiary referral center in the region, making this a complete overview of these patients, but this population may not represent the general uveitis population. A strength of this study is that our study, for determining definitions, adhered to the SUN Working Group criteria, thus contributing to more uniform reporting on uveitis outcomes. In addition, we collected prospective data on the development of glaucoma.

In conclusion, unilateral and bilateral (alternating or simultaneously affected) HLA-B27 associated AU are generally comparable, which indicates that it is probably the same disease entity. This study shows that unilateral and bilateral patients both have a good prognosis with regard to visual acuity and the development of ocular complications. It would be interesting to know the chance for unilateral HLA-B27 associated AU patients to become bilateral, but at this moment we cannot give an answer to this question. A longer prospective study is needed to provide clarity on this matter.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Chang JH, Wakefield D. Uveitis: a global perspective. Ocul Immunol Inflamm. 2002;10:263–279.
2. Jabs DA. Improving the Reporting of Clinical Case Series. Am J Ophthalmol. 2005;139:900–905.
3. Huang JJ, Gaudio PA. Ocular inflammatory disease and uveitis manual: diagnosis and treatment. Philadelphia, Wolters Kluwer, Lippincott Williams & Wilkins;2010.
4. Rothova A, Buitenhuis HJ, Meenken C, et al. Uveitis and systemic disease. Br J Ophthalmol. 76:137–141, 1992.
5. Zagora SL Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, AustraliaCorrespondencesophia.zagora@gmail.com, Symes R Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Yeung A Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Yates W Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia, Wakefield D School of Medical Sciences, Faculty of Medicine University of NSW, Sydney, NSW, Australia, McCluskey PJ Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; Sydney Eye Hospital, Sydney, NSW, Australia. Etiology and Clinical Features of Ocular Inflammatory Diseases in a Tertiary Referral Centre in Sydney, Australia. Ocul Immunol Inflamm. 2017;25:S107-S114.
6. Brewerton DA, Caffrey M, Nicholls A, Walters D, James DC. Acute anterior uveitis and HL-A 27. Lancet. 1973;302:994–996.
7. Foster CS, Vitale AT. Diagnosis and Treatment of Uveitis. 1st edition, Philadelphia, Pennsylvania, W. B. Saunders Company; 2002.
8. Mapstone R, Woodrow JC. HL-A 27 and acute anterior uveitis. Br J Ophthalmol. 1975;59:270-275.
9. Linssen A, Rothova A, Valkenburg HA, et al. The lifetime cumulative incidence of acute anterior uveitis in a normal population and its relation to ankylosing spondylitis and histocompatibility antigen HLA-B27. Invest Ophthalmol Vis Sci. 1991;32:2568–2578.
10. Nussenblatt RB, Whitcup SM. Uveitis, Fundamentals and Clinical Practice. 4th edition. St. Louis: Mosby Elsevier; 2010.
11. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-783.
12. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
13. Rothova A, van Veenedaal WG, Linssen A, Glasius E, Kijlstra A, de Jong PT. Clinical features of acute anterior uveitis. Am J Ophthalmol. 1987;103:137-145.
14. Monnet D, Breban M, Hudry C, Dougados M, Brézin AP. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. Ophthalmology. 2004;111:802-809.
15. Tuncer S, Adam YS, Urgancioglu M, Tugal-Tutkun I. Clinical features and outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis in a Turkish patient population. Ocul Immunol Inflamm. 2005;13:367-373.
16. Braakenburg AM, de Valk HW, de Boer J, Rothova A. Human leukocyte antigen-B27-associated uveitis: long-term follow-up and gender differences. Am J Ophthalmol. 2008;145:472-479.
17. Accorinti M, Iannetti L, Liverani M, Caggiano C, Gilardi M. Clinical features and prognosis of HLA B27-associated acute anterior uveitis in an Italian patient population. Ocul Immunol Inflamm. 2010;18:91-96.
18. Wang YQ, Lu XY, Wang YL, et al. Clinical analysis of 240 patients with HLA-B27 associated acute anterior uveitis. Eye Sci. 2012;27:169-172.
19. Karaconji T, Maconochie Z, McCluskey P. Acute anterior uveitis in Sydney. Ocul Immunol Inflamm. 2013;21:108-114.
20. Verhagen FH, Brouwer AH, Kuiper JJ, Ossewaarde-van Norel J, Ten Dam-van Loon NH, de Boer JH. Potential Predictors of Poor Visual Outcome in Human Leukocyte Antigen-B27-Associated Uveitis. Am J Ophthalmol. 2016;165:179-187.
21. Park SC, Ham DI. Clinical features and prognosis of HLA-B27 positive and negative anterior uveitis in a Korean population. J Korean Med Sci. 2009;24:722-728.
22. Power WJ, Rodriguez A, Pedroza-Seres M, Foster CS. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998;105:1646-1651.
23. Linssen A, Meenken C. Outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis. Am J Ophthalmol. 1995;120:351-361.
24. Torres S, Borges S, Artiles A. HLA-B27 and clinical features of acute anterior uveitis in Cuba. Ocul Immunol Inflamm. 2013;21:119-123.
25. Loh AR, Acharya NR. Incidence rates and risk factors for ocular complications and vision loss in HLA-B27-associated uveitis. Am J Ophthalmol. 2010;150:534-542.
26. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. Am J Ophthalmol. 1996;121:47-56.

5

Vision-related quality of life in herpetic anterior uveitis patients

Lisette Hoeksema & Leonoor I Los

PLoS One. 2014; 9: e85224

ABSTRACT

We investigated the vision-related quality of life (VR-QOL) and the prevalence and severity of depression in patients with herpetic anterior uveitis (AU). This study was conducted in 2012 at the ophthalmology department of the University Medical Center of Groningen (tertiary referral center). We selected patients from an existing uveitis database, all eligible patients were approached. Thirty-six of 66 (55%) patients with herpetic AU (herpes simplex virus or varicella zoster virus) participated, patients were 18 years or older. The diagnosis was made by clinical presentation or a positive anterior chamber tap. All patients received an information letter, informed consent form, National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), Beck Depression Inventory (BDI-II), Social Support List – Interactions (SSL-I), Social Support List – Discrepancies (SSL-D) and an additional questionnaire for gathering general information. Medical records were reviewed for clinical characteristics. Analyses were conducted on various patient and ocular characteristics. We compared our NEI VFQ-25 scores with those previously found in the literature. Our main outcome measures were VR-QOL, prevalence and severity of depression, social support and various patient and ocular characteristics that could influence the VR-QOL. We found that the NEI VFQ-25 mean overall composite score (OCS) was 88.1±10.6. Compared with other ocular diseases our OCS is relatively high, but lower than that found in a normal working population. The mean general health score was 59.0±19.0, this score is lower than in patients with other ocular diseases, except for untreated Behçet's patients. Depression was scarce, with only one patient (2.8%) having a moderate depression (BDI-II score of 21). We concluded that herpetic AU affects the VR-QOL in a moderate way. The prevalence of depression in our group of herpetic AU patients was low and therefore does not seem to indicate a need for specific screening and intervention measures in these patients.

INTRODUCTION

Anterior uveitis (AU) is the predominant form of uveitis and herpetic AU is the most frequently observed form of infectious AU.[1] Characteristics like dermatitis, keratitis, elevated intraocular pressure (IOP) and iris sector atrophy are seen in herpetic AU.[2] Also secondary complications, like glaucoma and cataract are reported.[3] Complications of uveitis can lead to irreversible loss of visual functioning.[4] Previous studies showed that 35% of uveitis patients in the Western society are significantly visually impaired or blind.[5]

Uveitis is seen in all age groups, and a substantial proportion of patients is of working age. During active uveitis, the inflammation and its treatment may – temporarily – affect visual functioning in such a way that it interferes with reading, computer work, driving, etc. Some patients may lose their job because of – recurrent – uveitis. Fear of a recurrence may cause increased stress levels, even when the uveitis is quiet. This may result in a decreased vision-related quality of life (VR-QOL) and an increased risk of developing a depression.

The purpose of this study is to evaluate the VR-QOL and the prevalence and severity of depression in a group of patients with a specific type of uveitis, i.e. herpetic AU (including herpes simplex virus (HSV) or varicella zoster virus (VZV) related AU). Previous research on a large group of uveitis patients found that uveitis patients reported a markedly poorer visual functioning and general health status than healthy subjects.[6] That study evaluated a non-homogeneous group of uveitis patients with different causes and manifestations of the disease. Since each cause and manifestation of uveitis may differ with regard to clinical characteristics and residual symptoms, it would also be of interest to examine the VR-QOL in the different uveitis entities separately. This may give valuable information for entity-related counseling of patients and may indicate the entity-related need for developing intervention strategies.

METHODS

Ethics Statement

The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study. The study was conducted according to the tenets of the Declaration of Helsinki.

Patients

The patients included in this study were selected from an existing database, containing uveitis patients who had been treated or are currently being treated for uveitis at the ophthalmology department of the University Medical Center of Groningen, which is a tertiary referral center. We included 66 patients with herpetic AU. All patients were 18 years or older. The diagnosis

was made by clinical presentation (keratitis - dendritic herpes branch - followed by AU, elevated intraocular pressure at presentation, iris sector atrophy developing over time and/or clear facial varicella zoster infection (ophthalmic nerve) with subsequent kerato-uveitis) or a positive anterior chamber tap for local antibody production or the presence of virus DNA by PCR. Patients with other forms or possible causes of uveitis were excluded.

Data

All 66 patients received an information letter and an informed consent form by mail. Included in this letter, they received the following questionnaires; the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), the Beck Depression Inventory (BDI-II), Social Support List – Interactions (SSL-I), Social Support List – Discrepancies (SSL-D) and an additional questionnaire for gathering general information. The patients were asked to complete the questionnaires at home, to sign the informed consent form and to return them by mail.

For measuring the VR-QOL, we used the validated Dutch version of the NEI VFQ-25. The NEI VFQ-25 has been developed by the National Eye Institute. This validated[7,8] self-administered questionnaire consists of 25 questions, with a total score and subscores ranging from 0 – 100. In this questionnaire, the score of 0 corresponds to the lowest and of 100 to the highest VR-QOL. There are 12 subscales, each consisting of one or more questions. These subscales are general health, general vision, ocular pain, near activities, distance activities, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving, color vision and peripheral vision.

The BDI-II is a validated[9] self-administered questionnaire consisting of 21 questions on how the patient feels and experiences things. Each question can be answered on a four-point scale ranging from 0 to 3. Subscores are added to create a total score. A total score of 0 to 13 corresponds with no depression, of 14 to 19 with a mild depression, of 20 to 28 with a moderately severe depression and of 29 to 63 with a severe depression. The SSL-I and SSL-D are questionnaires developed and validated by the University of Groningen (RUG). These questionnaires measure (1) social interactions between patients and persons with whom they interact and (2) if the received social support corresponds with the desired social support. They each consist of 34 four-choice questions, resulting in scores ranging from 1 – 4. A high SSL-I score corresponds with sufficient social support. A high SSL-D score corresponds with a deficiency in desired social support. The maximum score of the SSL-I is 136 and of the SSL-D it is 102.

The following information was gathered by the additional questionnaire: present activity of the uveitis, presence of other chronic diseases or diseases with a large impact (recent or in the past), medication use (ocular and other medication), history of depression and/or treatment, and need for visual revalidation. By reviewing medical records, we gathered the following information: present age, sex, unilateral or bilateral AU, systemic disease, follow-up time (defined as time

between the start of the first uveitis episode and the end of the last uveitis episode), total time of active disease, total number of uveitis episodes, remission time (defined as time between the end of the last uveitis episode and the date on the questionnaire), Snellen visual acuity (VA), ocular complications in history (elevated IOP, glaucoma, cataract, secondary cataract, keratitis, dry eyes, cystoid macular edema (CME), papillitis, scleritis and herpes zoster ophthalmicus (HZO)) and presence of active uveitis at the time of completing the questionnaire.

Active uveitis was defined as ≥0.5+ cells in the anterior chamber.[10] Transiently elevated IOP was defined as a measured IOP > 20 mmHg without pressure reducing medication. Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities. Dry eyes were defined as the presence of dry eye symptoms and need for artificial tears.

Statistics

Data were statistically analyzed using SPSS Statistics 20.0.0.1. For the comparison of continuous variables of two groups, we used the Mann-Whitney U test. For comparison of continuous variables of more than two groups, we used the Kruskal–Wallis one-way analysis and the Mann-Whitney U test for post hoc analysis with a Bonferroni correction, using a critical value of 0.05 divided by the number of tests conducted. Correlations were assessed with the Spearman's Rank Correlations test. For analyzing, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent. Statistical significance level was set at 0.05.

RESULTS

Thirty-six of 66 (55%) patients participated by filling out the questionnaires and returning them by mail. Table 1 summarizes the clinical characteristics of the 27 HSV and nine VZV AU patients. Males were slightly overrepresented in relation to females (58 versus 42%). Mean age of the HSV patients was 55.7±17.5 years and of VZV patients it was 63.7±15.1 years (p=0.201). Complications most frequently observed (in % of patients) were elevated IOP (69%), keratitis (64%), dry eyes (42%) and cataract (36%). We checked and confirmed that all complications developed after the diagnosis of AU. The mean (± SD) of the NEI VFQ-25, BDI-II, SSL-I and SSL-D scores are given in Table 1. Only one patient had a moderate depression (BDI-II score of 21) at the time of completing the questionnaires, for which he already received medical treatment.

Tables 2 and 3 give information on the mean (± SD) of the overall composite score (OCS) and the subscales of the NEI VFQ-25 in the total group. Also, differences herein related to various patient characteristics and ocular variables are presented. The mean OCS in the total group was 88.1±10.6 and the mean general health score was 59.0±19.0.

Table 1: clinical characteristics of herpetic AU patients and overall scores on questionnaires (N and (%) or Mean ± SD (range))

Number of patients	36
HSV / VZV	27 (75%) / 9 (25%)
Female / male	15 (42%) / 21 (58%)
Unilateral / bilateral	36 (100%) / 0 (0.0%)
Age at completing questionnaire (yrs)	57.7 ± 17.1 (25 – 88)
Follow-up time (yrs)	8.7 ± 12.4 (0.04-41.3)
Number of uveitis episodes	4.7 ± 5.4 (1 – 27)
Time of active uveitis (months)	5.1 ± 4.3 (1 – 17)
Remission time (yrs)	3.6 ± 2.5 (0.02 – 10.7)
Depression in past[a]	4 (11%)
Complications[b]	
- Elevated IOP	25 (69%)
- Keratitis	23 (64%)
- Dry eyes[c]	15 (42%)
- Cataract	13 (36%)
- HZO	8 (22%)
- Glaucoma	5 (14%)
- Secondary cataract	4 (11%)
- CME	2 (6%)
- Scleritis	0 (0%)
- Papillitis	0 (0%)
NEI VFQ-25 OCS[d]	88.1 ± 10.6 (51.7 – 97.6)
BDI-II score	3.7 ± 4.5 (0 – 21)
SSL-I score	74.0 ± 17.8 (34 – 105)
SSL-D score	45.3 ± 16.1 (34 – 102)

AU: anterior uveitis, HSV: Herpes Simplex Virus, VZV: Varicella Zoster Virus, IOP: Intraocular Pressure, CME: Cystoid Macular Edema, HZO: Herpes Zoster Ophthalmicus, OCS: Overall Composite Score, BDI: Beck Depression Inventory, SSL-I: Social Support List - Interactions, SSL-D: Social Support List - Discrepancies.
[a] Diagnosed by a physician and medically treated.
[b] Developed during follow-up AU.
[c] Medication needed.
[d] Average of vision-targeted subscale scores, without general health subscore.

Table 2: NEI VFQ-25 subscale scores and overall composite score (OCS), Mean ± SD

		GH (n=36)	GV (n=36)	OP (n=36)	NA (n=36)	DA (n=36)	VSSF (n=35)	VSMH (n=36)	VSRD (n=36)	VSD (n=36)	D (n=30)	CV (n=35)	PV (n=34)	OCS[a] (n=36)
Total group (n=36)		**59.0±19.0**	**76.1±9.3**	**73.3±22.8**	**87.7±16.7**	**92.6±12.6**	**97.1±8.1**	**84.9±14.4**	**84.0±21.9**	**97.7±7.1**	**87.1±16.2**	**97.1±10.1**	**91.2±20.3**	**88.1±10.6**
Sex	- Male (n=21)	61.9±23.2	78.1±8.7	81.5±17.1	87.7±18.0	92.5±11.8	96.3±9.2	85.4±11.4	88.1±12.8	97.6±6.0	88.3±15.4	96.3±12.2	91.3±23.3	89.4±10.3
	- Female (n=15)	55.0±10.4	73.3±9.6	61.7±25.2	87.8±15.4	92.8±14.0	98.3±6.5	84.2±18.3	78.3±30.1	97.8±8.6	84.6±18.2	98.3±6.5	91.1±15.8	86.2±11.1
		p=0.19	*p=0.14*	***p=0.02***	*p=0.99*	*p=0.54*	*p=0.30*	*p=0.61*	*p=0.58*	*p=0.35*	*p=0.50*	*p=0.71*	*p=0.59*	*p=0.24*
Present age (yrs)	- <45 (n=8)	56.3±17.7	80.0±0.0	75.0±16.4	96.9±6.2	97.9±3.9	100.0±0.0	88.3±5.2	96.9±5.8	100.0±0.0	95.8±7.0	100.0±0.0	96.4±9.4	93.3±3.1
	- 45 – 65 (n=14)	62.5±19.0	75.7±11.6	73.2±28.1	83.3±22.2	89.3±17.7	96.4±10.3	81.3±19.1	82.1±22.8	97.0±7.0	85.8±19.2	94.6±14.5	88.5±30.0	86.2±14.7
	- >65 (n=14)	57.1±20.6	74.3±9.4	72.3±21.5	86.9±13.0	92.9±8.6	96.4±7.6	86.6±12.5	78.6±24.7	97.0±9.0	84.0±15.7	98.2±6.7	91.1±12.4	87.1±7.9
		p=0.68	p=0.35	p=0.93	p=0.15	p=0.39	p=0.44	*p=0.83*	*p=0.04*[b]	*p=0.40*	*p=0.25*	*p=0.53*	*p=0.51*	*p=0.24*
HSV/VZV	- HSV (n=27)	61.1±20.0	77.0±9.1	76.4±22.3	89.2±14.6	93.5±11.4	98.6±5.4	87.3±13.1	87.5±18.0	98.8±5.0	88.7±16.2	98.1±6.8	93.0±13.5	89.8±8.9
	- VZV (n=9)	52.8±15.0	73.3±10.0	63.9±22.9	83.3±22.4	89.8±16.0	93.1±12.7	77.8±16.6	73.6±29.6	94.4±11.0	80.6±15.5	94.4±16.7	86.1±33.3	83.0±14.0
		p=0.23	p=0.31	*p=0.12*	*p=0.59*	*p=0.44*	*p=0.06*	***p=0.03***	*p=0.07*	*p=0.06*	*p=0.14*	*p=0.70*	*p=0.98*	*p=0.09*
Activity uveitis	- Active (n=4)	56.3±12.5	75.0±10.0	71.9±21.3	75.0±28.9	79.2±21.0	87.5±17.7	76.6±19.3	78.1±18.8	95.8±4.8	75.0±16.7	87.5±25.0	68.8±47.3	79.6±19.6
	- Inactive (n=32)	59.4±19.8	76.3±9.4	73.4±23.3	89.3±14.5	94.3±10.5	98.4±5.3	85.9±13.7	84.8±22.4	97.9±7.3	88.4±15.6	98.4±6.2	94.2±12.6	89.2±8.9
		p=0.70	*p=0.82*	*p=0.78*	*p=0.22*	*p>0.05*	***p=0.03***	*p=0.23*	*p=0.30*	***p=0.04***	*p=0.11*	*p=0.18*	*p=0.14*	*p=0.27*
Uveitis episodes[c]	- 1 episode (n=11)	61.4±17.2	74.5±12.9	61.4±21.3	86.4±15.5	95.5±7.8	96.6±8.1	85.8±12.8	75.0±28.5	96.2±10.1	88.4±13.8	95.5±10.1	95.0±10.5	86.2±8.7
	- >1 episode (n=22)	56.8±20.7	77.3±7.0	77.8±22.5	88.6±18.6	90.9±14.8	97.6±8.5	84.7±16.1	89.2±17.8	98.5±5.5	87.3±18.1	97.6±10.9	90.5±24.3	89.2±12.1
		p=0.65	*p=0.36*	***p=0.04***	*p=0.52*	*p=0.47*	*p=0.51*	*p=0.92*	*p=0.06*	*p=0.44*	*p=0.96*	*p=0.26*	*p=0.95*	*p=0.11*

NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, HSV: Herpes Simplex Virus, VZV: Varicella Zoster Virus. Mean scores ± one standard deviation are given.

[a] Average of vision-targeted subscale scores, without GH. [b] Bonferroni correction, significance level p<0.017. [c] Missing data in three patients.

Table 3: NEI VFQ-25 subscale scores and overall composite score (OCS), Mean ± SD

		GH (n=36)	GV (n=36)	OP (n=36)	NA (n=36)	DA (n=36)	VSSF (n=35)	VSMH (n=36)	VSRD (n=36)	VSD (n=36)	D (n=30)	CV (n=35)	PV (n=34)	OCS[a] (n=36)
Dry eyes	- No (n=21)	58.3±19.9	77.1±9.6	79.2±21.8	89.7±16.9	93.3±12.3	97.5±6.5	86.0±14.6	88.1±18.7	98.4±5.7	89.4±15.7	97.5±7.7	94.7±13.4	90.1±9.9
	- Yes (n=15)	60.0±18.4	74.7±9.2	65.0±22.3	85.0±16.7	91.7±13.4	96.7±10.0	83.3±14.5	78.3±25.2	96.7±8.8	82.5±16.9	96.7±12.9	86.7±26.5	85.3±11.3
		p=0.88	p=0.46	***p=0.04***	*p=0.12*	*p=0.61*	*p=0.93*	*p=0.39*	*p=0.08*	*p=0.38*	*p=0.16*	*p=0.78*	*p=0.25*	***p=0.04***
Elevated IOP	- No (n=11)	68.2±16.2	80.0±8.9	73.9±21.3	94.7±8.6	98.5±3.4	98.9±3.8	89.8±5.8	92.0±12.8	99.2±2.5	93.8±12.4	97.7±7.5	95.5±10.1	92.1±5.6
	- Yes (n=25)	55.0±19.1	74.4±9.2	73.0±23.8	84.7±18.6	90.0±14.2	96.4±9.4	82.8±16.6	80.5±24.2	97.0±8.3	84.7±16.9	96.9±11.2	89.1±23.6	86.3±11.8
		p=0.05	*p=0.11*	*p=0.99*	*p=0.11*	***p=0.04***	*p=0.52*	*p=0.40*	*p=0.10*	*p=0.55*	*p=0.09*	*p=0.97*	*p=0.55*	*p=0.12*
Keratitis	- No[b] (n=20)	53.8±16.8	75.0±8.9	71.9±19.0	89.2±16.5	92.1±11.9	96.1±9.4	85.0±13.5	81.9±23.8	97.1±7.8	85.3±16.1	97.4±11.5	90.3±24.5	87.4±10.8
	- Yes[c] (n=16)	65.6±20.2	77.5±10.0	75.0±27.4	85.9±17.4	93.2±13.7	98.4±6.3	84.8±16.0	86.7±19.6	98.4±6.3	88.9±16.6	96.9±8.5	92.2±15.1	88.9±10.7
		p=0.08	*p=0.46*	*p=0.37*	*p=0.58*	*p=0.38*	*p=0.24*	*p=0.87*	*p=0.47*	*p=0.27*	*p=0.42*	*p=0.50*	*p=0.87*	*p=0.39*
Other disease[d]	- No (n=17)	61.8±17.9	76.5±7.9	74.3±22.3	88.7±13.5	96.1±6.0	99.2±3.1	85.3±11.5	83.8±24.1	96.1±9.8	91.3±9.1	100.0±0.0	95.0±10.4	89.5±6.7
	- Yes (n=19)	56.6±20.1	75.8±10.7	72.4±23.8	86.8±19.5	89.5±15.9	95.4±10.4	84.5±17.0	84.2±20.3	99.1±2.6	83.8±19.6	94.7±13.4	88.2±25.5	86.8±13.2
		p=0.42	p=0.77	p=0.86	p=0.76	p=0.26	p=0.20	p=0.56	p=0.96	p=0.48	p=0.51	*p=0.10*	*p=0.57*	*p=0.79*
Visual acuity[e,f]	- <0.5 (n=10)	67.5±16.9	70.0±10.5	68.8±29.0	75.8±21.0	85.0±20.0	93.8±13.5	75.6±22.9	68.8±32.9	95.8±10.6	80.6±20.8	92.5±16.9	77.5±32.2	80.3±16.4
	- ≥0.5 (n=22)	54.5±19.9	78.2±8.5	74.4±20.6	90.9±13.1	94.7±7.1	98.2±4.5	88.1±7.9	89.2±13.0	98.1±5.7	89.6±14.2	98.8±5.5	96.3±9.2	90.6±5.4
		p=0.082	***p=0.027***	*p=0.649*	***p=0.021***	*p=0.230*	*p=0.552*	*p=0.174*	*p=0.053*	*p=0.607*	*p=0.256*	*p=0.174*	***p=0.031***	*p=0.149*
Treatment uveitis[g]	- No (n=16)	62.5±18.3	77.5±10.0	74.2±19.6	91.7±12.5	95.8±7.5	97.7±6.8	87.1±11.3	86.7±26.8	97.4±8.5	91.7±12.7	96.9±8.5	96.9±8.5	90.2±8.5
	- Yes (n=20)	56.3±19.7	75.0±8.9	72.5±25.5	84.6±19.2	90.0±15.2	96.7±9.2	83.1±16.6	81.9±17.4	97.9±6.0	83.6±18.0	97.4±11.5	86.1±26.0	86.4±12.0
		p=0.32	p=0.46	p=0.96	p=0.25	p=0.21	p=0.79	p=0.65	p=0.05	p=0.87	p=0.14	p=0.50	p=0.14	p=0.20

NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, IOP: Intraocular Pressure. Mean scores ± one standard deviation are given.

[a] Average of vision-targeted subscale scores, without GH. [b] No keratitis in history or keratitis in history without residuals. [c] Keratitis with residuals. [d] Medical chronic condition or medical condition with large impact, recent or in the past, except for uveitis. [e] At least one eye with Snellen visual acuity <0.5. Measured with Snellen chart within six months before or after completing the NEI VFQ-25. [f] Missing data in four patients. [g] Treatment of the uveitis and/or complications at the moment of completing the NEI VFQ-25.

Female patients scored significantly lower on ocular pain (indicating that they experienced more pain or discomfort around or in the eye). VZV patients scored lower on all subscales and on the OCS compared to HSV patients, but only the difference in scores on vision specific mental health reached significance. Patients with active uveitis had significantly lower vision specific social functioning and vision specific dependency scores. They also had lower distance activities scores, but this did not reach significance. Patients who experienced just one uveitis episode had significantly lower ocular pain scores (more pain) than patients who experienced multiple uveitis episodes. Dry eye patients scored significantly lower on ocular pain (more pain) and on the OCS. Patients with transiently or persistently elevated IOP had significantly lower distance activities scores. Patients with a Snellen VA of less than 0.5 in at least one eye, scored lower on the OCS and on all subscales, but only the scores on general vision, near activities and peripheral vision reached significance.

Age, keratitis and uveitis treatment showed no significant correlation with any of the NEI VFQ-25 outcomes. Also, patients with or without other chronic diseases (in our group: diabetes, respiratory diseases, hypercholesterolemia, hypertension and back pain) or diseases with a large impact (in our group: multiple brain infarcts, cancer, psoriasis vulgaris, depression, antithrombin III deficiency, **polymyalgia-rheumatica**, hypothyroidism and cardiovascular diseases (recent or in the past)) did not score significantly different on the NEI VFQ-25 scales, including the general health subscale.

Table 4 shows the results of the Spearman's Rank Correlations tests between studied variables and NEI VFQ-25 subscale scores and OCS. Age at completing the questionnaire and general vision, near activities and vision specific role difficulties were negatively correlated. LogMAR VA of the uveitic eye was negatively correlated with near activities and peripheral vision. Remission time was positively correlated with peripheral vision and central vision. The BDI score was negatively correlated with general health, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving and OCS. There was no significant correlation between the subscale scores and OCS and logMAR VA of the healthy eye, duration of active uveitis, total of uveitis episodes, follow-up time, SSL-I score and SSL-D score. There was no significant correlation between the BDI-II score and the SSL-I score or the SSL-D score.

Table 4: Spearman's Rank Correlations between studied variables and NEI VFQ-25 subscale scores and OCS

	GH	GV	OP	NA	DA	VSSF	VSMH	VSRD	VSD	D	CV	PV	OCS[a]
Age at completing questionnaire	-0.035	**-0.360**	0.097	**-0.371**	-0.220	-0.192	0.057	**-0.407**	-0.113	-0.325	-0.008	-0.206	-0.267
	p=0.84	**p=0.03**	p=0.57	**p=0.03**	p=0.20	p=0.27	p=0.74	**p=0.01**	p=0.51	p=0.08	p=0.96	p=0.24	p=0.12
LogMAR VA uveitic eye	0.115	-0.273	-0.099	**-0.352**	-0.201	0.029	-0.206	-0.218	-0.116	-0.085	-0.090	**-0.383**	-0.219
	p=0.53	p=0.12	p=0.59	**p=0.04**	p=0.26	p=0.87	p=0.25	p=0.22	p=0.52	p=0.67	p=0.63	**p=0.03**	p=0.22
LogMAR VA fellow eye	-0.107	-0.261	0.139	-0.243	-0.003	0.049	-0.138	-0.164	-0.122	-0.079	0.173	0.042	-0.130
	p=0.56	p=0.15	p=0.45	p=0.18	p=0.99	p=0.80	p=0.45	p=0.37	p=0.51	p=0.70	p=0.35	p=0.82	p=0.48
Number of uveitis episodes	-0.008	0.110	0.170	-0.045	-0.271	-0.005	-0.051	0.185	0.142	0.030	0.084	-0.244	0.098
	p=0.97	p=0.54	p=0.34	p=0.81	p=0.13	p=0.98	p=0.78	p=0.30	p=0.43	p=0.88	p=0.65	p=0.19	p=0.59
Duration of active uveitis	-0.028	0.099	0.143	0.009	-0.193	0.036	0.107	0.011	0.056	-0.058	0.070	-0.155	0.054
	p=0.88	p=0.58	p=0.43	p=0.96	p=0.28	p=0.85	p=0.55	p=0.95	p=0.76	p=0.77	p=0.71	p=0.41	p=0.76
Follow-up time	0.115	0.144	0.145	0.013	-0.201	0.086	0.061	0.185	0.123	0.068	0.164	-0.250	0.139
	p=0.51	p=0.41	p=0.41	p=0.94	p=0.25	p=0.63	p=0.73	p=0.29	p=0.48	p=0.72	p=0.35	p=0.16	p=0.43
Remission time	-0.092	0.061	-0.071	0.294	0.291	0.274	0.092	0.046	0.283	-0.075	**0.387**	**0.429**	0.107
	p=0.59	p=0.72	p=0.68	p=0.08	p=0.09	p=0.11	p=0.59	p=0.79	p=0.09	p=0.69	**p=0.02**	**p=0.01**	p=0.53
BDI-II score	**-0.433**	-0.255	-0.261	-0.131	-0.134	**-0.485**	**-0.493**	**-0.348**	**-0.414**	**-0.558**	-0.066	-0.175	**-0.456**
	p=0.01	p=0.15	p=0.14	p=0.46	p=0.45	**p=0.004**	**p=0.003**	**p=0.04**	**p=0.02**	**p=0.002**	p=0.71	p=0.32	**p=0.007**
SSL-I score	-0.081	-0.211	0.065	-0.143	0.184	0.091	0.088	0.059	0.105	0.237	0.003	0.179	-0.006
	p=0.67	p=0.25	p=0.73	p=0.44	p=0.32	p=0.63	p=0.64	p=0.75	p=0.57	p=0.24	p=0.99	p=0.34	p=0.97
SSL-D score	-0.024	0.046	-0.060	0.022	-0.066	-0.143	-0.174	-0.197	0.021	-0.356	-0.018	-0.077	-0.130
	p=0.90	p=0.81	p=0.75	p=0.91	p=0.73	p=0.45	p=0.35	p=0.29	p=0.91	p=0.07	p=0.93	p=0.69	p=0.49

NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, VA: Visual Acuity, BDI: Beck Depression Inventory, SSL-I: Social Support List - Interactions, SSL-D: Social Support List – Discrepancies.

[a] Average of vision-targeted subscale scores, without GH.

DISCUSSION

We found that in general NEI VFQ-25 subscale scores and the OCS were reasonably high in herpetic AU patients. We found a mean OCS of 88.1 which means that the majority of patients scored between the best possible (100.0) and the second best score (75.0). General health is the only subscale that is not included in the OCS. The mean general health score was lower than the means of the other subscales, namely 59.0. However, this still means that the majority of patients scored their general health between 'good' (50.0) and 'very good' (75.0). Depression was scarce in our study group, with only one patient having a moderate depression.

To give an overall idea of the height of the scores in our patient group in relation to those previously found in healthy persons and in patients with ocular disease, we constructed Table 5. Interestingly, Hirneiss et al. who obtained NEI VFQ-25 scores in a normal working population as well as in subpopulations thereof with and without ocular disease, found that general health scores were lower in the subgroup with ocular disease.[11] The general health scores of his total group and subpopulations were higher than in our patient group. Studies on patients with noninfectious ocular inflammatory disease and Birdshot chorioretinopathy showed general health scores comparable with our general health score.[12,13] Highest general health scores were achieved in patients with acute posterior vitreous detachment.[14] Untreated Behçet's disease patients had the lowest general health scores, which is not surprising because of the commonly associated systemic manifestations in this entity.[15]

The overall composite score (OCS) is low in untreated Behçet's disease and Birdshot chorioretinopathy.[13,15] Unfortunately, OCS was not given in the study on bilateral age-related macular degeneration patients, but from the subscale scores, it can be derived that it will have been lowest in this patient group.[16] Schiffman et al. also found a relatively low OCS (± 63.0) in a large group of uveitis patients. Their data was presented graphically and therefore it is difficult to derive exact values on NEI VFQ-25 scores. Because of this, we did not include that study in Table 5.[6] In our patient group, OCS was relatively high, but lower than those in the working population and in acute posterior vitreous detachment patients.[11,14] A possible explanation for the relatively high OCS in our study is that all our patients had a unilateral disease.

Looking at subgroup analyses in our study group (Tables 2, 3 and 4), age at the moment of completing the questionnaires seemed to be of no influence on total NEI VFQ-25 scores. When evaluating correlations between age and the NEI VFQ-25 subscales, it seems that general vision, near vision and performing tasks nearby become more difficult with age. Also, older patients more often indicate that accomplishing things is getting more difficult because of reduced vision and they feel limited because of their vision. Surprisingly, a history of keratitis seemed to have no effect on VR-QOL, whereas we would expect that residuals of keratitis would influence visual functioning and thereby some of the vision related subscales of the NEI VFQ-25. Also, any

medical chronic condition or medical condition (other than ophthalmologic) with a large impact seemed to have no influence on the NEI VFQ-25 scores. Our study and studies summarized in Table 5 seem to suggest that ophthalmic disease itself may influence general health scores.

In our study, significantly more pain or discomfort in or around the eye was reported by female patients and patients who experienced only one uveitis episode. Previous clinical and epidemiological studies show that women are at an increased risk of developing chronic pain and some evidence suggests that women may experience more severe pain. Multiple biopsychosocial mechanisms may contribute to these gender differences in experienced pain, including sex hormones, endogenous opioid function, genetic factors, pain coping and catastrophizing and gender roles.[17] A possible explanation for the difference in reported pain between patients with one versus multiple uveitis episodes, could be the fact that herpes viruses are neurotrophic, and can destroy sensible nerve fibers. This is well-known for corneal sensibility[18] but may also apply to other structures within the eye. Presumably, repeated herpes activity will have a cumulative effect. Another possibility is that coping strategies may change with a longer duration of the disease.

VZV patients scored somewhat lower on all subscales and OCS compared with HSV patients, and this was not due to age or VA. Eight out of nine (89%) VZV patients had had HZO, and it is therefore possible that the lower scores are at least partly due to the occurrence of dermatitis or post-herpetic neuralgia in these patients. Lukas et al. showed that herpes zoster, and especially post-herpetic neuralgia, is associated with increased levels of pain that have a significant impact on QOL scores.[19] In our study, dry eye patients had a lower OCS, which was mainly due to more ocular pain. Li et al. also reported that VR-QOL in dry eye patients can be impaired.[20]

Patients with a Snellen VA of less than 0.5 in at least one eye, were more likely to have lower VR-QOL scores, compared to patients with a Snellen VA of more than 0.5 at both eyes. Of these, only the scores on the subscales general vision, near activities and peripheral vision reached significance. The VA of the uveitic eye was correlated with near activities and peripheral vision scores (Table 4). The VA in the fellow eye does not seem to have any influence on the VR-QOL. The fact that we did not find major significant differences based on VA, was possibly due to the fact that most patients had a relatively good VA in both eyes.

In our study, we identified only one patient (2.8%) with a moderate depression. By comparison, de Graaf et al. found a 12–month prevalence of any mood disorder (i.e. depression and other mood disorders) of 6.1% in the Netherlands between 1996 and 2009.[21] Qian et al. reported that 28/104 (26.9%) of patients with ocular inflammatory disease screened positive for depression, using the BDI-II questionnaire. These depressed patients scored far lower on the composite VFQ-25 score than non-depressed patients.[12] In our study, patients with a higher BDI-II score were also likely to score lower on the VR-QOL. We found that a higher BDI-II score was negatively correlated with

Table 5: NEI VFQ-25 subscale scores and OCS compared with literature

Study	Mean age ± SD (yrs)	Group composition	GH	GV	OP	NA	DA	VSSF	VSMH	VSRD	VSD	D	CV	PV	OCS[a]
			Mean (SD)												
Hoeksema n=36	58 ± 17	Herpetic anterior uveitis	59.0 (19.0)	76.1 (9.3)	73.3 (22.8)	87.7 (16.7)	92.6 (12.6)	97.1 (8.1)	84.9 (14.4)	84.0 (21.9)	97.7 (7.1)	87.1 (16.2)	97.1 (10.1)	91.2 (20.3)	88.1 (10.6)
Hirneiss 2010[11] n=619	42 ± 9	Normal working population - Total group	73.0 (18.1)	78.6 (15.7)	85.4 (16.6)	91.9 (13.1)	91.8 (11.3)	97.9 (9.0)	87.4 (10.5)	92.8 (13.8)	98.4 (5.6)	88.7 (10.6)	97.9 (9.3)	93.3 (15.0)	91.1 (7.4)
Hirneiss 2010[11] n= 511	42 ± 9	Normal working population - Without ocular disease	79.9 (17.4)	79.0 (15.9)	87.6 (15.1)	92.3 (13.0)	92.1 (11.4)	98.1 (8.2)	87.8 (10.0)	93.4 (13.3)	98.5 (5.5)	88.8 (10.6)	98.0 (8.7)	93.4 (14.6)	91.6 (7.1)
Hirneiss 2010[11] n=108	43	Normal working population - Only with ocular disease	68.6 (20.7)	79.1 (15.9)	75.1 (19.2)	90.2 (13.6)	90.6 (10.7)	96.8 (12.3)	85.3 (12.5)	89.7 (15.6)	97.9 (5.8)	88.4 (10.4)	97.3 (11.6)	92.5 (16.7)	88.8 (8.3)
Qian 2011[12] n=104	41	Noninfectious ocular inflammatory disease	60.3 -	72.8 -	73.9 -	79.2 -	78.8 -	89.9 -	70.8 -	74.2 -	84.9 -	77.4 -	94.9 -	81.3 -	79.7 -
Sakai 2013[15] n=20	45 ± 14	Behçet uveitis untreated	31.3 (13.8)	48.0 (10.1)	78.8 (12.9)	53.3 (4.9)	60.6 (6.8)	69.6 (10.2)	43.4 (15.3)	53.2 (14.0)	77.3 (12.7)	58.3 (12.2)	82.5 (11.8)	75.0 (16.2)	63.6 (8.9)
Sakai 2013[15] n=20	45 ± 14	Behçet uveitis infliximab[b]	77.5 (11.2)	82.0 (11.1)	98.1 (4.6)	87.4 (11.9)	85.2 (10.8)	90.0 (12.6)	92.6 (13.7)	92.6 (10.2)	95.4 (9.9)	85.0 (18.5)	92.5 (11.8)	93.8 (11.1)	90.3 (8.7)
Kuiper 2013[13] n=105	59.5 (median)	Birdshot chorioretinopathy	61.6 -	63.8 -	75.1 -	68.6 -	70.3 -	84.5 -	71.2 -	64.5 -	84.2 -	66.8 -	80.2 -	67.6 -	71.0 -
Cahill 2005[16] n=70	76.4 ± 5.6	Bilateral severe AMD	- -	31.4 (15.8)	81.8 (20.3)	29.4 (18.6)	38.8 (24.7)	58.4 (28.1)	34.1 (25.1)	38.2 (27.1)	42.7 (29.7)	16.1 (31.3)	67.5 (27.7)	66.8 (25.1)	- -
Schweitzer 2011[14] n=84	Males: 64.5 ± 6.6 Females: 62.1 ± 7.6	Acute posterior vitreous detachment[c]	80.56 (15.95)	85.77 (10.94)	89.58 (12.85)	89.58 (10.89)	94.43 (8.27)	99.11 (3.43)	91.78 (9.75)	95.68 (8.62)	99.40 (3.01)	87.87 (14.56)	99.11 (6.07)	95.53 (11.09)	93.47 (6.20)

NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25. GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score.

[a] Average of vision-targeted subscale scores, without GH. [b] 12 months after receiving infliximab. [c] Six week follow-up visit.

general health, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving and OCS. A possible explanation for the higher prevalence of depression in the study of Qian et al., is that they included patients with severe posterior and panuveitis in addition to AU patients. Qian et al. also mention that inadequate emotional support is a predictor of depression. In our study, the amount of social support appeared to have no influence on VR-QOL or depression.

The main shortcoming of our study is its modest sample size. Our sample size is considered adequate for overall analyses[22], but it may be too limited for all subgroup analyses, resulting in an underreporting of possibly relevant associations. Also, only 55% of herpetic uveitis patients participated in the present study, which may have resulted in a selection bias. Furthermore, our patients were seen at a tertiary referral center and therefore this population may not represent the general uveitis population.

In conclusion, herpetic AU affects the VR-QOL, but only in a moderate way. The NEI VFQ-25 subscale scores and OCS are reasonably good. The prevalence of depression in our group of herpetic AU patients was low and therefore does not seem to indicate a need for specific screening and intervention measures in this specific patient group.

ACKNOWLEDGMENTS

None

REFERENCES

1 Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, et al. (2009) Uveitis subtypes in a German interdisciplinary uveitis center—analysis of 1916 patients. J Rheumatol 36: 127–136.

2 Jap A, Chee SP (2011) Viral anterior uveitis. Curr Opin Ophthalmol 22: 483-488.

3 Wensing B, Relvas LM, Caspers LE, Valentincic NV, Stunf S, et al. (2011) Comparison of rubella virus- and herpes virus-associated anterior uveitis: clinical manifestations and visual prognosis. Ophthalmol 118: 1905-1910.

4 Huang JJ, Gaudio PA (2010) Ocular inflammatory disease and uveitis manual: diagnosis and treatment. Philadelphia, Wolters Kluwer, Lippincott Williams & Wilkins pp. 41-60.

5 Rothova A, Suttorp van Schulten MS, Frits Treffers W, Kijlstra A (1996) Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol 80: 332-336.

6 Schiffman RM, Jacobsen G, Whitcup SM (2001) Visual functioning and general health status in patients with uveitis. Arch Ophthalmol 119: 841-849.

7 Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, et al. (1998) Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol 116: 1496-1504.

8 Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, et al. (2001) National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 119: 1050-1058.

9 Arnau RC, Meagher MW, Norris MP, Bramson R (2001) Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychol 20: 112-119.

10 Jabs DA, Nussenblatt RB, Rosenbaum JT (2005) Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140: 509-516.

11 Hirneiss C, Schmid-Tannwald C, Kernt M, Kampik A, Neubauer AS (2010) The NEI VFQ-25 vision-related quality of life and prevalence of eye disease in a working population. Graefes Arch Clin Exp Ophthalmol 248: 85-92.

12 Qian Y, Glaser T, Esterberg E, Acharya NR (2012) Depression and visual functioning in patients with ocular inflammatory disease. Am J Ophthalmol 153: 370-378.

13 Kuiper JJ, Missotten T, Baarsma SG, Rothova A (2013) Vision-related quality of life in patients with birdshot chorioretinopathy. Acta Ophthalmol 91: e329-331.

14 Schweitzer KD, Eneh AA, Hurst J, Bona MD, Rahim KJ, et al. (2011) Visual function analysis in acute posterior vitreous detachment. Can J Ophthalmol 46: 232-236.

15 Sakai T, Watanabe H, Kuroyanagi K (2013) Health- and vision-related quality of life in patients receiving infliximab therapy for Behcet uveitis. Br J Ophthalmol 97: 338-342.

16 Cahill MT, Banks AD, Stinnett SS, Toth CA (2005) Vision-related quality of life in patients with bilateral severe age-related macular degeneration. Ophthalmol 112: 152-158.

17 Bartley EJ, Fillingim RB (2013) Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth 111: 52-58.

18 Pavan-Langston D (1995) Herpes zoster ophthalmicus. Neurology 45: S50-51.

19 Lukas K, Edte A, Bertrand I (2012) The impact of herpes zoster and post-herpetic neuralgia on quality of life: patient-reported outcomes in six European countries. Z Gesundh Wiss 20: 441-451.

20 Li M, Gong L, Chapin WJ, Zhu M (2012) Assessment of vision-related quality of life in dry eye patients. Invest Ophthalmol Vis Sci 53: 5722-5727.

21 de Graaf R, Ten Have M, van Gool C, van Dorsselaer S (2012) Prevalence of mental disorders, and trends from 1996 to 2009. Results from NEMESIS-2. Tijdschr Psychiatr 54: 27-38.

22 Mangione CM (2000) NEI-VFQ Scoring Algorithm. Version 2000

6

Vision-related quality of life in patients with inactive HLA-B27-associated-spectrum anterior uveitis

Lisette Hoeksema & Leonoor I Los

PLoS One. 2016; 11: e0146956

ABSTRACT

We investigated the vision-related quality of life (VR-QOL) in patients with HLA-B27 associated anterior uveitis (AU). The study was conducted in 2012 at the ophthalmology department of the University Medical Center of Groningen. We included AU patients who were HLA-B27 positive and/or were diagnosed by a rheumatologist with an HLA-B27 associated systemic disease. Sixty-one of 123 (50%) adult patients participated. All patients filled-out the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), Beck Depression Inventory (BDI-II), social support lists and an additional questionnaire for gathering general information. Medical records were reviewed for clinical characteristics. Analyses were conducted on various patient and ocular characteristics. We compared our NEI VFQ-25 scores with those previously found in the literature. Our main outcome measures were VR-QOL scores and their associations with various general patient and ocular characteristics. We found that the NEI VFQ-25 mean overall composite score was 88.9±8.8, which is relatively high, but lower than that found in a normal working population. The mean general health score was 47.4±20.8, which is lower than in patients with other ocular diseases. Patients with a systemic disease scored significantly lower on general health and VR-QOL, compared to patients without a systemic disease. Patients with a depression (6/59 (10%)) frequently had ankylosing spondylitis (5/6 patients) and they scored significantly worse on VR-QOL. We concluded that patients with HLA-B27 associated AU have a relatively high VR-QOL. However, the presence of a systemic disease is associated with lower VR-QOL and general health scores. In addition, depression is associated with a lower VR-QOL.

INTRODUCTION

Anterior uveitis (AU) is the most common form of uveitis and it is commonly associated with HLA-B27 associated diseases, such as ankylosing spondilitis, Crohn's disease, reactive arthritis and psoriasis. Also, HLA-B27 positivity without apparent systemic disease may be associated with AU.[1] This type of uveitis is often recurrent and it can occur uni- or bilaterally. Complications like high intraocular pressure, glaucoma, cataract, posterior synechiae and dry eyes are seen in HLA-B27 associated AU.[2] The visual acuity (VA) can decrease temporarily or permanently because of recurrent inflammation and complications of AU. All these characteristics can affect a patient's quality of life.

Previous studies indicated a poorer visual functioning and a lower general health status in uveitis patients compared to healthy subjects.[3] Most studies evaluated VR-QOL in heterogenous groups of uveitis patients.[3-5] Qian et al. found an inverse correlation between National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) scores and best-corrected visual acuity (BCVA) and between NEI VFQ-25 and Beck Depression Inventory II (BDI-II) scores in patients with non-infectious ocular inflammatory disease.[4] Schiffman et al. reported that non-infectious uveitis patients with more severe uveitis have poorer visual functioning and general health status than patients with milder disease.[3] A few studies looked at VR-QOL in specific uveitis patient groups. Kuiper et al. observed that VR-QOL is impaired in patients with birdshot chorioretinopathy and that VR-QOL composite scores were related to BCVA, but not related to age or duration of uveitis.[6] In a previous study, we found that VR-QOL is only mildly reduced in herpetic AU.[7] These findings suggest differences in impact on VR-QOL in various uveitis entities. For proper patient counseling, it would therefore be useful to examine VR-QOL in the different uveitis entities separately and to investigate the ocular and patient characteristics that may influence VR-QOL.

The purpose of the present study is to evaluate the VR-QOL in a group of patients with an HLA-B27 associated AU. We hope to identify clinical features that are associated with a lower quality of life in this patient group. Identifying such features may help to develop targeted screening and intervention measures in the future.

METHODS

The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study, since the study is not a medical scientific study with people as defined in the *Medical Research Involving Human Subjects Act*. The study was conducted according to the tenets of the Declaration of Helsinki.

Patients

We selected all patients from an existing database, containing uveitis patients who are currently being treated or who have been treated for uveitis at the ophthalmology department of the University Medical Center Groningen, which is a tertiary referral center.

We identified 123 adult (18 years or older) patients with HLA-B27 associated AU. Patients were HLA-B27 positive and/or were clinically diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. Patients with ankylosing spondylitis were diagnosed following the Assessment of SpondyloArthritis international Society classification criteria (ASAS criteria). Therefore patients with sacroiliitis on imaging and ≥ one axial spondyloarthritis criteria, have not always been tested for HLA-B27 positivity.[8] Patients with other forms or possible causes of uveitis were excluded.

Data

All suitable 123 patients received the following questionnaires by mail: the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), the Beck Depression Inventory (BDI-II), Social Support List – Interactions (SSL-I), Social Support List – Discrepancies (SSL-D) and an additional questionnaire for gathering general information. They also received an information letter and an informed consent form. Patients could complete the questionnaires and sign the informed consent form at home and return them by mail. We contacted all patients by phone, to ask if they needed assistance in filling out the questionnaire. All patients were literate.

In this study, we used the Dutch version of the NEI VFQ-25. This validated[9,10] questionnaire measures the VR-QOL and has been developed by the National Eye Institute. This self-administered questionnaire consists of a base set of 25 vision-targeted questions representing 11 vision-related subscales, plus an additional single-item general health rating question. The overall composite score (OCS) is the average of the vision-targeted subscale scores, without the general health score. In this questionnaire, a score of 0 corresponds to the lowest and of 100 to the highest VR-QOL. There are 12 subscales, each consisting of one or more questions. These subscales are general health, general vision, ocular pain, near activities, distance activities, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving, color vision and peripheral vision.

The BDI-II is a validated[11] self-administered questionnaire evaluating how a patient feels and experiences things. It consists of 21 questions and each question can be answered on a four-point scale ranging from 0 to 3. All scores are added to provide a total score, with a maximum of 36. The total score gives an estimation of the severity of an existing depression. A total score of 0 to 13 corresponds with no depression, of 14 to 19 with a mild depression, of 20 to 28 with a moderately severe depression and of 29 to 63 with a severe depression.

The SSL-I and SSL-D are questionnaires developed and validated by the University of Groningen. They each consist of 34 four-choice questions, resulting in scores ranging from 1 – 4. The SSL-I questionnaire measures the social interactions between patients and persons with whom they interact. The maximum score is 136, a high SSL-I score corresponds with sufficient social support. The SSL-D questionnaire measures if the received social support corresponds with the desired social support. The maximum score is 102, a high SSL-D score corresponds with a deficiency in desired social support.

The additional questionnaire gave us the following information: whether the uveitis was active at the time of completing the questionnaire, medical history (including chronic diseases or diseases with a large impact, recently or in the past), medication use (ocular and other medication) and history of depression and the need for treatment.

The following information was collected by examining medical records: current age, sex, uni- or bilateral AU, presence of a systemic disease, follow-up (time between the start of the first uveitis episode and the end of the last uveitis episode), total number of uveitis episodes, total time of active disease in months, remission time (time between the end of the last uveitis episode and the date on the questionnaire), Snellen VA, ocular complications (elevated intraocular pressure (IOP), glaucoma, cataract, secondary cataract, dry eyes and current treatment for dry eyes, cystoid macular edema (CME), papillitis, scleritis and posterior synechiae) and present activity of the uveitis. To evaluate a possible bias by inclusion, the following data were collected from the patients who did not return the questionnaire: visual acuity at the end of follow-up, duration of follow-up, presence of systemic disease, bilaterality of disease (simultaneously bilateral or alternating between the right and left eye) and ocular complications.

Active uveitis was defined as ≥0.5+ cells in the anterior chamber.[12] Transiently elevated IOP was defined as a measured IOP > 20 mmHg without pressure reducing medication. Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities. Dry eyes were defined as the presence of dry eye symptoms and the need for artificial tears at any time.

Statistics

Data were statistically analyzed using SPSS Statistics 20.0.0.1. The Mann-Whitney U test was used to compare continuous variables of two groups. The Kruskal–Wallis one-way analysis was used to compare continuous variables of more than two groups and the Mann-Whitney U test for post hoc analysis with a Bonferroni correction, using a critical value of 0.05 divided by the number of tests conducted. Correlations were assessed with the Spearman's Rank Correlations test. For analyzing, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent. Statistical significance level was set at 0.05.

RESULTS

Sixty-one of 123 (50%) patients filled out the questionnaires and returned them by mail. Table 1 gives an overview of the clinical characteristics of these patients. Male to female ratio was 3:2. Mean age was 55 ± 12 years. The group contained approximately the same percentage of patients with unilateral and bilateral disease. Since only a small minority (n=2) of the patients had active AU at the time of completing the questionnaires, these were excluded from the analyses. Four (7%) patients indicated that they had had a depression in the past, diagnosed by a physician and medically treated. Forty-three (73%) patients were tested for HLA-B27 positivity and tested positive (100%), sixteen (27%) patients were not tested for HLA-B27, but were diagnosed with an HLA-B27 associated systemic disease by a rheumatologist. A systemic disease was present in 34 out of 59 (58%) patients and ankylosing spondylitis was the most common (44%) (Table 1). Ocular complications most frequently observed (in % of patients) were posterior synechiae (63%), elevated IOP (37%), dry eyes (29%), cataract (27%) and CME (14%). We checked and confirmed that all complications developed after the diagnosis of AU. The mean (± SD) of the NEI VFQ-25, BDI-II, SSL-I and SSL-D scores are given in Table 1. The BDI-II scores showed that six patients had a mild depression at the time of filling out the questionnaire; five out of these six patients (83%) had ankylosing spondylitis.

Table 1 also gives an overview of the clinical characteristic of the patients who did not fill out the questionnaires, which was available in 56 out of 64 patients. Patients who filled-out the questionnaire, had a slightly longer follow-up (13,6±9,7 versus 9,9±9,6 years, p=0,04) and were older (55±12 versus 46±15) as compared to patients who did not fill-out the questionnaires.

The mean (± SD) of the OCS and the subscales of the NEI VFQ-25 in relation to diverse patients' characteristics and ocular variables are shown in Tables 2 and 3. The mean OCS in the total group was 88.9±8.8 and the mean general health score was 47.4±20.8.

LogMAR VA higher than 0.15 (Snellen VA less than 7/10; a higher LogMAR VA corresponds to a lower Snellen VA), treatment of the uveitis at the time of completing the NEI VFQ-25, presence of a systemic disease and presence of a depression at the time of completing the NEI VFQ-25 were patients' characteristics that were highly associated with a lower NEI VFQ-25 OCS and/or NEI VFQ-25 subscales. LogMAR VA higher than 0.15 in at least one eye, was correlated to significantly lower scores on general vision, distance activities, vision specific role difficulties, vision specific dependency and color vision. Treatment of the AU and treatment of ophthalmic complications at the moment of completing the NEI VFQ-25 were related to lower scores on the subscales, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, color vision and peripheral vision. Patients with a systemic disease scored significantly lower on the OCS and on the subscales general health, ocular pain, distance activities, vision specific mental health and peripheral vision. Depression

Table 1: clinical characteristics of HLA-B27 associated AU patients and overall scores on questionnaires (N and (%) or Mean ± SD (range))

	Patients who filled out the questionnaires	Patients who did not fill out the questionnaires	p
Number of patients	59	56	-
Female / male	23 (39%) / 36 (61%)	22 (39%) /34 (61%)	0.973
Age at completing questionnaire / study (yrs)	54 ± 12 (28 – 81)	46 ± 15 (19 – 90)	**0.001**
Unilateral / bilateral*	28 (47%) / 31 (53%)	21 (38%) / 35 (63%)	0.280
Total uveitis episodes	7.3 ± 6.5 (1 – 40)	6.8 ± 6.3 (1 – 24)	0.579
Time of active uveitis (months)	5.8 ± 5.0 (1 – 30)	5.5 ± 6.0 (1 – 30)	0.753
Follow-up time (yrs)	13.6 ± 9.7 (0.03 – 36.0)	9.9 ± 9.6 (0.02 – 29.8)	**0.039**
Remission time (yrs)	3.2 ± 2.8 (0.00 - 12.0)	3.4 ± 3.4 (0.09 – 15.4)	0.721
Depression in past†	4 (7%)	-	-
Present depression	6 (10%)	-	-
HLA-B27 tested (% of total group)	43 (73%)	44 (79%)	0.477
HLA-B27 positive (% of tested)	43 (100%)	44 (100%)	-
HLA-B27 not tested (% of total group)‡	16 (27%)	12 (21%)	0.477
Systemic disease	34 (58%)	27 (48%)	0.312
- Ankylosing spondylitis	26 (44%)	22 (39%)	-
- Reactive arthritis	3 (5%)	0 (0%)	-
- Crohn / Colitis ulcerosa	2 (3%)	2 (4%)	-
- Other	3 (5%)	3 (5%)	-
Ocular complications§	53 (90%)	46 (82%)	0.234
- Posterior synechiae	37 (63%)	29 (52%)	-
- Elevated IOP	22 (37%)	25 (45%)	-
- Dry Eyes‖	17 (29%)	11 (20%)	-
- Cataract	16 (27%)	16 (29%)	-
- CME	8 (14%)	7 (13%)	-
- Secondary cataract	4 (7%)	2 (4%)	-
- Papillitis	3 (5%)	3 (5%)	-
- Glaucoma	2 (3%)	1 (2%)	-
NEI VFQ-25 OCS#	88.9 ± 8.8 (53.7 – 98.0)	-	-
BDI-II score	4.7 ± 5.3 (0 – 19)	-	-
SSL-I score	76.2 ± 15.3 (34 – 104)	-	-
SSL-D score	42.1 ± 11.5 (34 – 80)	-	-

AU: anterior uveitis, IOP: Intraocular Pressure, CME: Cystoid Macular Edema, OCS: Overall Composite Score, BDI: Beck Depression Inventory, SSL-I: Social Support List - Interactions, SSL-D: Social Support List - Discrepancies.
* Simultaneously bilateral or alternating between the right and left eye.
† Diagnosed by a physician and medically treated.
‡ All patients that have not been tested for HLA-B27 positivity (n=17), were diagnosed with an HLA-B27 associated systemic disease by a rheumatologist.
§ Developed during follow-up AU and in at least one eye.
‖ Medication needed.
Average of vision-targeted subscale scores, without general health subscore.

at the time of completing the NEI VFQ-25 was correlated to significantly worse scores on the OCS and on the subscales general vision, near activities, distance activities, vision specific social functioning and driving. These patients also scored lower on all other subscales, except color vision, but these subscales did not reach significance.

The patients' characteristics that were moderately associated with lower NEI VFQ-25 OCS and/or NEI VFQ-25 subscales were older age, female gender, multiple uveitis episodes, bilateral AU, dry eyes and presence of CME. Younger patients (<45 years) scored significantly better (p=0.026) on near activities compared to older patients (≥45 years). Post hoc analyses showed that near activity scores in patients <45 years versus those aged 45 – 65 years and patients <45 years versus those aged >65 years significantly differ (p=0.008 and p=0.049, respectively), whereas near activities scores did not significantly differ for patients between 45 - 65 years and patients >65 years (p=0.714). Female patients scored significantly worse on driving. Patients who experienced only one uveitis episode had significantly higher general vision scores, compared with patients who experienced multiple uveitis episodes. Patients with bilateral AU scored significantly lower on ocular pain (indicating that they experienced more pain or discomfort around or in the eye). Patients with dry eyes scored significantly lower on ocular pain and on the OCS. Patients with CME scored lower on vision specific dependency and color vision. Elevated IOP, posterior synechiae and treatment of the systemic disease at the moment of completing the questionnaire showed no significant correlation with any of the NEI VFQ-25 outcomes.

The results of the Spearman's Rank Correlations tests between NEI VFQ-25 subscale scores and OCS and of various patient and ocular characteristics are given in Table 4. Positive correlations were seen with age at completing the questionnaire and remission time. Age at completing the questionnaire was positively correlated to ocular pain and vision specific mental health. Remission time was positively correlated with general vision and vision specific mental health. Negative correlations were seen with higher LogMAR VA of the worst eye, follow-up time, BDI-II score and SSL-D score.

Higher LogMAR VA of the worst eye was negatively correlated with general vision and vision specific dependency. Follow-up time was negatively correlated with general vision and vision specific dependency. The BDI-II score was negatively correlated with the OCS and almost all subscales, except general vision and color vision. The SSL-D score was negatively correlated with the OCS and near activities, distance activities and vision specific role difficulties. Positive and negative correlations were seen with higher LogMAR VA of the best eye. Higher LogMAR VA of the best eye was negatively correlated with distance activities, vision specific dependency, peripheral vision and positively correlated with ocular pain. There was no significant correlation between the subscale scores or OCS and the number of uveitis episodes, duration of active uveitis and SSL-I score. The BDI-II score was positively correlated with the SSL-D score (r=0.486, p<0.001).

Table 2: NEI VFQ-25 subscale scores and ocular composite score (OCS), Mean ± SD

		GH (n=58)	GV (n=58)	OP (n=59)	NA (n=59)	DA (n=59)	VSSF (n=59)	VSMH (n=59)	VSRD (n=59)	VSD (n=59)	D (n=54)	CV (n=59)	PV (n=59)	OCS* (n=59)
Total group (n=59)		**47.4±20.8**	**78.3±10.8**	**73.1±20.3**	**88.0±15.2**	**90.8±12.3**	**97.2±8.7**	**88.7±9.2**	**86.4±17.4**	**97.5±8.9**	**85.3±14.2**	**99.6±3.3**	**94.1±12.6**	**88.9±8.8**
Sex	- Male (n=36)	46.5±23.3	76.7±10.1	71.9±21.6	88.0±14.3	91.2±12.6	97.2±9.5	88.7±9.9	86.8±17.7	97.0±10.6	88.9±12.1	99.3±4.2	95.1±11.7	88.9±9.4
	- Female (n=23)	48.9±16.3	80.9±11.5	75.0±18.5	88.0±16.8	90.2±12.0	97.3±7.5	88.6±8.1	85.9±17.4	98.2±5.6	79.8±15.7	100.0±0.0	92.4±14.0	88.9±7.9
		p=0.582	p=0.155	p=0.618	p=0.648	p=0.618	p=0.825	p=0.720	p=0.822	*p=0.906*	***p=0.025***	*p=0.424*	*p=0.386*	*p=0.675*
Present age (yrs)	- < 45 (n=14)	58.9±21.0	82.9±10.7	70.5±21.1	96.4±7.1	94.6±7.0	99.1±3.3	87.9±6.7	90.2±16.4	100.0±0.0	87.5±10.2	100.0±0.0	98.2±6.7	91.6±4.6
	- 45 – 65 (n=34)	43.9±19.8	77.6±10.9	72.1±20.7	84.6±17.1	89.7±13.6	96.0±11.0	87.9±9.8	85.7±17.2	96.6±10.9	84.4±14.7	99.3±4.3	92.6±14.5	87.6±9.7
	- > 65 (n=11)	43.2±19.7	74.5±9.3	79.5±18.8	87.9±13.1	89.4±13.0	98.9±3.8	92.0±9.7	84.1±20.2	97.0±7.7	85.2±18.5	100.0±0.0	93.2±11.7	89.3±9.4
		p=0.060	*p=0.143*	*p=0.504*	***p=0.026***	*p=0.546*	*p=0.668*	*p=0.288*	*p=0.523*	*p=0.244*	*p=0.887*	*p=0.692*	*p=0.363*	*p=0.588*
Uveitis episodes†	- 1 episode (n=6)	50.0±22.4	86.7±10.3	75.0±20.9	88.9±10.1	98.6±3.4	100.0±0.0	90.6±9.5	85.4±20.0	100.0±0.0	85.0±9.1	100.0±0.0	100.0±0.0	91.9±5.1
	- > 1 episode (n=52)	47.1±21.0	77.3±10.6	72.8±20.7	87.8±15.9	89.9±12.7	96.9±9.2	88.6±9.2	87.0±17.1	97.3±9.4	85.8±14.6	99.5±3.5	94.2±11.7	88.7±9.1
		p=0.734	***p=0.048***	*p=0.866*	*p=0.747*	*p=0.059*	*p=0.343*	*p=0.618*	*p=0.891*	*p=0.343*	*p=0.594*	*p=0.734*	*p=0.216*	*p=0.499*
Laterality	- Unilateral (n=28)	50.0±19.6	79.3±11.7	80.4±18.5	89.6±14.6	92.0±9.8	97.3±7.1	90.8±7.5	88.4±16.6	98.2±6.6	88.1±11.0	100.0±0.0	95.5±9.8	90.9±7.2
	- Bilateral (n=31)	45.2±21.8	77.4±10.0	66.5±20.0	86.6±15.8	89.8±14.2	97.2±10.1	86.7±10.2	84.7±18.2	96.8±10.7	82.4±16.7	99.2±4.5	92.7±14.7	87.0±9.7
		p=0.208	*p=0.539*	***p=0.009***	*p=0.416*	*p=0.877*	*p=0.626*	*p=0.096*	*p=0.401*	*p=0.211*	*p=0.281*	*p=0.342*	*p=0.580*	*p=0.052*
Visual acuity‡,§	- > 0.15 (n=7)	46.4±9.4	68.6±10.7	75.0±22.8	77.4±20.8	77.4±20.8	91.1±18.7	81.3±15.3	69.6±23.8	88.1±20.9	81.9±23.2	96.4±9.4	85.7±19.7	79.5±16.1
	- ≤ 0.15 (n=42)	47.0±21.1	78.5±10.4	71.7±20.3	89.7±12.6	92.5±9.4	98.2±5.9	89.6±7.8	88.1±15.1	98.4±5.6	86.9±13.1	100.0±0.0	94.6±11.8	89.9±6.4
		p=0.961	***p=0.023***	*p=0.683*	*p=0.079*	***p=0.041***	*p=0.146*	*p=0.160*	***p=0.027***	***p=0.002***	*p=0.880*	***p=0.014***	*p=0.140*	*p=0.170*
Systemic disease	- No (n=25)	61.5±18.0	80.8±9.3	79.5±21.6	92.0±10.1	95.0±7.2	99.5±2.5	91.5±7.8	89.5±14.3	99.7±1.7	89.1±12.7	100.0±0.0	98.0±6.9	91.9±5.5
	- Yes (n=34)	37.5±16.6	76.5±11.5	68.4±18.3	85.0±17.6	87.7±14.2	95.6±11.0	86.6±9.6	84.2±19.3	95.8±11.5	82.5±14.8	99.3±4.3	91.2±14.9	86.6±10.0
		p<0.001	*p=0.121*	***p=0.045***	*p=0.243*	***p=0.044***	*p=0.101*	***p=0.039***	*p=0.392*	*p=0.063*	*p=0.079*	*p=0.391*	*p=0.041*	***p=0.027***

NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score. Average of vision-targeted subscale scores, without GH. † Missing data in one patient. ‡ At least one eye with LogMAR visual acuity > 0.15. Measured with Snellen chart and converted to LogMAR visual acuity, measured within six months before or after completing the NEI VFQ-25. § Missing data in ten patients.

Table 3: NEI VFQ-25 subscale scores and ocular composite score (OCS), Mean ± SD

		GH (n=58)	GV (n=58)	OP (n=59)	NA (n=59)	DA (n=59)	VSSF (n=59)	VSMH (n=59)	VSRD (n=59)	VSD (n=59)	D (n=54)	CV (n=59)	PV (n=59)	OCS* (n=59)
Dry eyes	- No (n=42)	47.0±22.9	78.1±11.5	69.6±21.1	87.3±15.6	89.7±12.6	96.1±10.1	87.2±9.8	83.9±18.6	96.6±10.4	84.9±13.4	99.4±3.9	92.9±13.8	87.6±9.2
	- Yes (n=17)	48.4±14.3	78.8±8.9	81.6±16.0	89.7±14.3	93.6±11.2	100.0±0.0	92.3±6.5	92.6±12.5	99.5±2.0	86.5±16.4	100.0±0.0	97.1±8.3	92.1±6.6
		p=0.711	*p=0.802*	***p=0.041***	*p=0.477*	*p=0.180*	*p=0.076*	*p=0.064*	*p=0.114*	*p=0.260*	*p=0.495*	*p=0.525*	*p=0.282*	***p=0.049***
Elevated IOP	- No (n=37)	49.3±21.6	78.4±8.7	74.0±20.9	89.0±12.0	91.7±10.4	98.3±6.0	90.5±7.7	89.2±14.8	98.9±4.5	85.4±11.0	100.0±0.0	96.0±9.3	90.1±6.6
	- Yes (n=22)	44.0±19.2	78.1±14.0	71.6±19.7	86.4±19.7	89.4±15.0	95.5±11.9	85.5±10.6	81.8±20.7	95.1±13.3	85.3±18.4	98.9±5.3	91.0±16.4	86.8±11.4
		p=0.432	p=0.848	p=0.780	p=0.645	p=0.953	p=0.252	p=0.061	p=0.195	p=0.111	p=0.438	p=0.195	p=0.253	p=0.573
CME	- No (n=51)	47.5±21.0	78.8±11.0	71.6±20.6	88.2±14.6	90.5±11.4	97.8±6.5	89.1±8.1	87.0±16.6	98.5±5.2	84.4±14.1	100.0±0.0	95.1±10.0	89.3±7.4
	- Yes (n=8)	46.9±20.9	75.0±9.3	82.8±16.3	86.5±19.4	92.7±17.5	93.8±17.7	85.9±14.8	82.8±23.1	90.6±20.1	93.1±13.4	96.9±8.8	87.5±23.1	86.4±15.4
		p=0.912	*p=0.367*	*p=0.145*	*p=0.862*	*p=0.170*	*p=0.859*	*p=0.838*	*p=0.766*	***p=0.034***	*p=0.092*	***p=0.012***	*p=0.506*	*p=0.603*
Posterior synechiae†	- No (n=21)	53.6±19.8	80.0±11.0	73.8±16.3	89.3±17.7	91.7±12.6	97.6±7.5	89.6±8.0	87.5±17.7	98.0±5.8	84.9±15.5	100.0±0.0	92.9±14.0	89.6±8.1
	- Yes (n=37)	45.1±19.7	77.8±10.5	73.0±22.7	87.6±13.8	90.8±12.0	97.3±9.4	88.5±9.7	86.8±16.7	97.7±9.8	85.9±13.6	99.3±4.1	95.3±11.5	88.9±9.0
		p=0.123	p=0.450	p=0.993	p=0.163	p=0.493	p=0.903	*p=0.740*	*p=0.657*	*p=0.699*	*p=0.903*	*p=0.451*	*p=0.476*	*p=0.827*
Current depression	- No (n=53)	49.0±20.4	79.2 ±10.4	74.3±20.0	89.8±14.4	92.3±11.2	98.1±7.9	89.2±9.0	87.5±17.3	97.8±8.8	86.6±13.8	99.5±3.4	94.8±12.4	89.8±8.3
	- Yes (n=6)	33.3±20.4	70.0±11.0	62.5±22.4	72.2±13.6	77.8±14.6	89.6±12.3	84.4±10.3	77.1±16.6	94.4±10.1	73.3±13.7	100.0±0.0	87.5±13.7	80.9±9.2
		p=0.106	***p=0.044***	*p=0.167*	***p=0.004***	***p=0.012***	***P0.003***	*p=0.212*	*p=0.080*	*p=0.134*	***p=0.046***	*p=0.737*	*p=0.076*	***p=0.022***
Treatment uveitis†,‡	- No (n=49)	49.0±21.0	78.8±10.3	73.2±21.0	88.6±14.1	92.2±10.5	98.2±6.3	89.9±7.8	89.3±14.9	99.0±4.0	86.6±12.8	100.0±0.0	95.9±9.3	90.0±6.9
	- Yes (n=9)	40.6±18.6	75.0±14.1	69.4±15.5	83.3±20.8	82.4±17.9	91.7±16.5	80.6±11.9	69.4±21.8	88.9±19.5	78.1±19.9	97.2±8.3	83.3±21.7	81.7±14.1
		p=0.421	*p=0.338*	*p=0.646*	*p=0.551*	*p=0.069*	***p=0.039***	***p=0.018***	***p=0.005***	***p=0.003***	*p=0.260*	***p=0.020***	***p=0.033***	*p=0.075*
Treatment systemic disease§	- No (n=15)	40.0±12.7	74.7±11.9	70.0±18.8	87.2±14.7	87.8±14.4	97.5±7.0	88.3±8.5	89.2±17.6	97.2±6.8	83.9±15.6	100.0±0.0	93.3±11.4	88.1±9.1
	- Yes (n=19)	35.5±19.2	77.9±11.3	67.1±18.3	83.3±19.8	87.7±14.5	94.1±13.4	85.2±10.5	80.3±20.1	94.7±14.2	81.3±14.4	98.7±5.7	89.5±17.3	85.4±10.8
		p=0.451	p=0.411	p=0.710	p=0.638	p=1.000	p=0.514	p=0.394	p=0.146	p=0.883	p=0.443	p=0.374	p=0.632	p=0.395

NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, IOP: Intraocular Pressure, CME: Cystoid Macular Edema.

* Average of vision-targeted subscale scores, without GH. † Missing data in one patient. ‡ Treatment of the uveitis and/or treatment of ophthalmic complications at the moment of completing the NEI VFQ-25.

§ Only patients with systemic disease (n=35).

Table 4: Spearman's Rank Correlations between studied variables and NEI VFQ-25 subscale scores and OCS

	GH	GV	OP	NA	DA	VSSF	VSMH	VSRD	VSD	D	CV	PV	OCS*
Age at completing questionnaire	-0.252 p=0.056	-0.242 p=0.067	**0.288 p=0.027**	-0.178 p=0.179	-0.154 p=0.243	0.065 p=0.627	**0.275 p=0.035**	-0.055 p=0.679	-0.143 p=0.280	-0.003 p=0.984	-0.116 p=0.383	-0.118 p=0.375	0.052 p=0.697
LogMAR VA best eye	0.019 p=0.894	-0.258 p=0.073	**0.341 p=0.016**	-0.045 p=0.757	**-0.355 p=0.011**	-0.042 p=0.775	0.014 p=0.922	-0.011 p=0.940	**-0.290 p=0.041**	-0.054 p=0.719	-0.257 p=0.071	**-0.351 p=0.012**	-0.036 p=0.802
LogMAR VA worst eye	0.136 p=0.358	**-0.359 p=0.012**	0.262 p=0.069	-0.169 p=0.245	-0.248 p=0.086	-0.060 p=0.681	-0.023 p=0.877	-0.027 p=0.853	**-0.405 p=0.004**	-0.114 p=0.3452	-0.247 p=0.087	-0.249 p=0.085	-0.102 p=0.485
Total of uveitis episodes	-0.139 p=0.303	-0.139 p=0.303	-0.122 p=0.362	-0.103 p=0.440	-0.073 p=0.588	0.044 p=0.740	-0.034 p=0.798	0.008 p=0.950	-0.082 p=0.539	-0.053 p=0.707	-0.099 p=0.458	0.030 p=0.823	-0.091 p=0.495
Duration of active uveitis	-0.171 p=0.207	-0.160 p=0.239	-0.175 p=0.192	-0.246 p=0.065	-0.186 p=0.166	-0.155 p=0.249	0.035 p=0.794	-0.117 p=0.387	-0.125 p=0.353	-0.093 p=0.514	-0.025 p=0.856	-0.121 p=0.368	-0.177 p=0.189
Follow-up time	-0.170 p=0.201	**-0.341 p=0.009**	-0.145 p=0.272	-0.122 p=0.357	-0.076 p=0.567	-0.016 p=0.905	-0.055 p=0.680	0.031 p=0.816	**-0.277 p=0.034**	0.019 p=0.891	0.015 p=0.908	-0.125 p=0.346	-0.118 p=0.373
Remission time	0.123 p=0.358	**0.265 p=0.044**	0.136 p=0.305	0.121 p=0.362	0.067 p=0.613	0.177 p=0.180	**0.423 p=0.001**	0.141 p=0.286	0.181 p=0.171	-0.174 p=0.207	0.154 p=0.244	0.127 p=0.339	0.251 p=0.055
BDI-II score	**-0.342 p=0.009**	-0.238 p=0.071	**-0.338 p=0.009**	**-0.367 p=0.004**	**-0.403 p=0.002**	**-0.386 p=0.003**	**-0.275 p=0.035**	**-0.385 p=0.003**	**-0.272 p=0.037**	**-0.422 p=0.001**	-0.008 p=0.953	**-0.298 p=0.022**	**-0.486 p<0.001**
SSL-I score	0.073 p=0.589	0.125 p=0.354	-0.059 p=0.662	-0.064 p=0.634	-0.073 p=0.590	-0.073 p=0.590	-0.084 p=0.533	-0.066 p=0.627	0.101 p=0.454	-0.110 p=0.431	-0.154 p=0.251	-0.061 p=0.652	-0.082 p=0.546
SSL-D score	-0.115 p=0.399	-0.094 p=0.489	-0.140 p=0.302	**-0.275 p=0.041**	**-0.279 p=0.038**	**-0.223 p=0.099**	-0.208 p=0.125	**-0.324 p=0.015**	-0.114 p=0.405	-0.253 p=0.071	0.158 p=0.246	-0.105 p=0.442	**-0.329 p=0.013**

NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25, GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, VA: Visual Acuity, BDI: Beck Depression Inventory, SSL-I: Social Support List - Interactions, SSL-D: Social Support List – Discrepancies.
* Average of vision-targeted subscale scores, without GH.

DISCUSSION

In general, the NEI VFQ-25 OCS and subscale scores were relatively high in patients with HLA-B27 associated AU. The mean OCS was 88.9 in the total group. The best score to achieve on each question was 100 and the second best score 75 or 80. This means that most patients scored between the best and second best scores. The OCS is the average of all vision-targeted subscale scores, only excluding general health. The mean general health score was rather low, in comparison to the vision-targeted subscales, namely 47.4. This means that the majority of patients scored their general health between 'fair' (25.0) and 'good' (50.0). Six (10%) of patients had a mild depression.

Patients who were currently being treated for uveitis or ophthalmic complications had lower scores on vision specific social functioning, vision specific mental health, vision specific role difficulties and vision specific dependency. This means that these patients are more worried and frustrated by their eyesight and they need more help because of their eyesight. In our patients, a history of dry eyes seemed to have no effect on the VR-QOL, patients with dry eyes in their history even scored higher on ocular pain (indicating that they experienced less pain or discomfort around or in the eye). In seeming contrast, Li et al. reported that VR-QOL in dry eye patients was significantly impaired. The difference is probably due to the fact that in Li's study, all patients had dry eyes at the moment of completing the NEI VFQ-25.[13] Whereas in our study, only one patient was being treated for dry eyes at the time of completing the NEI VFQ-25 and 16 patients had a history of dry eyes. So, it seems that current dry eye symptoms and signs may affect VR-QOL outcomes, whereas a history of dry eyes does not. Further, we observed that patients with a longer follow-up time scored worse and patients with a longer remission time scored better on general vision. Longer remission times also seemed beneficial for vision specific mental health.

Subgroup analyses further show that younger patients (<45 years) score better on near activities compared to older patients (≥45 years; Table 2). This is probably due to beginning presbyopia in the older patient group. Having had more than one uveitis episode seems to affect general vision, since patients who experienced only one uveitis episode scored significantly higher on general vision, compared to patients who experienced multiple uveitis episodes. However, by the Spearman's Rank Correlations test we could not demonstrate an additional effect of the number of episodes. Higher LogMAR VA in either the best or the worst seeing eye was correlated to lower scores on a number of subscales, but not to a lower OCS. The latter was possibly due to the fact that most patients had a relatively good VA in both eyes, and thus differences in VA between eyes and patients were relatively small.

To compare the scores of the NEI VFQ-25 in our patient group to patients with other ocular diseases and healthy persons, and to gain a better insight in the meaning of the scores, we

composed Table 5. Based on the vision-targeted subscales, it can be derived that the mean OCS is lowest in patients with age-related macular degeneration.[14] Hirneiss et al. obtained NEI VFQ-25 scores in a normal working population as well as in subpopulations thereof with and without ocular disease. They found that the mean OCS was highest in the working population without ocular disease (91.6), though the difference with the subgroup with ocular disease (mean OCS of 88.8) was small. Our mean OCS (88.9) was comparable to that observed by Hirneiss in the subgroup with ocular disease.[15] Previous studies on non-infectious uveitis found lower mean OCS scores (79.7 and 80.3, respectively) and median OCS score (62.0) than that in our patient group.[4,5,16] A possible explanation is that these studies had included various forms of uveitis, and not just AU. This assumption seems to be confirmed by the relatively low mean OCS (71.0) observed in a study on patients with birdshot chorioretinopathy, which is classified as posterior uveitis.[6] In a previous study, conducted in the same region, we observed that herpetic AU patients are comparable with patients with HLA-B27 associated AU, with regard to the mean OCS (88.1).[7] Based on this comparison, we can conclude that patients with AU associated with either HLA-B27 or herpes, score relatively high on VR-QOL.

In contrast, the mean general health score (47.4) in our patient group was relatively low. By comparison, mean general health scores in a normal working population with and without ocular disease were 68.6 and 79.9, respectively.[15] Patients with non-infectious uveitis (general health of 60.3 and 59.1)[4,5] and birdshot chorioretinopathy (general health of 61.6) [6], scored lower than the normal working population and slightly higher than our patient group. Herpetic AU patients from the same referral area as in the present study, also scored higher (59.0).[7] Our results indicate that this may be due to the presence of an HLA-B27 associated systemic disease. In our group, patients with a systemic disease had a mean general health score of 37.5 versus 61.5 in patients without a systemic disease. The latter is comparable to other noninfectious uveitis patients.[4,5] Also, patients with a systemic disease scored lower on VR-QOL. In line with this, studies on the health-related quality of life (Short-Form-36 Health Survey) in ankylosing spondylitis patients, find an influence of systemic disease on reported physical and mental health as well.[17-19] In addition, Kempen et al. suggest that uveitis may have additional health impact over and above its effect on vision, perhaps via symptoms of inflammation unmeasured by visual acuity, side effects of treatment, the impact of associated systemic disease, or a combination thereof.[20]

In our patient group, patients had a mean BDI-II score of 4.7 (SD ± 5.3; range 0 – 19) and six (10%) patients had a mild depression at the time of completing the questionnaire. The majority of these, (5/6 (83%)) had ankylosing spondylitis, suggesting that the presence of a systemic disease has a higher influence on this outcome than the presence of AU. Previous studies on HLA-B27 associated diseases, give similar prevalence numbers, since they describe a clinically relevant depression in 12.3% of 171 HLA-B27 associated AU patients and in 14.8% of 55 ankylosing spondylitis patients, respectively.[21,22] Depression may have a negative effect on VR-QOL, since patients with a depression scored significantly lower on the NEI VFQ-25 (Tables 3 and 4). Qian et al. reported

Table 5: NEI VFQ-25 subscale scores and OCS compared with literature

Study	Mean age ± SD (yrs)	Group composition	GH	GV	OP	NA	DA	VSSF	VSMH	VSRD	VSD	D	CV	PV	OCS*
			Mean (SD)												
Hoeksema	55 ± 12	HLA-B27 associated	47.4	78.3	73.1	88.0	90.8	97.2	88.7	86.4	97.5	85.3	99.6	94.1	88.9
n=59		anterior uveitis	(20.8)	(10.8)	(20.3)	(15.2)	(12.3)	(8.7)	(9.2)	(17.4)	(8.9)	(14.2)	(3.3)	(12.6)	(8.8)
Hirneiss 2009[15]	42 ± 9	Normal working population	73.0	78.6	85.4	91.9	91.8	97.9	87.4	92.8	98.4	88.7	97.9	93.3	91.1
n=619		- Total group	(18.1)	(15.7)	(16.6)	(13.1)	(11.3)	(9.0)	(10.5)	(13.8)	(5.6)	(10.6)	(9.3)	(15.0)	(7.4)
Hirneiss 2009[15]	42 ± 9	Normal working population	79.9	79.0	87.6	92.3	92.1	98.1	87.8	93.4	98.5	88.8	98.0	93.4	91.6
n= 511		- Without ocular disease	(17.4)	(15.9)	(15.1)	(13.0)	(11.4)	(8.2)	(10.0)	(13.3)	(5.5)	(10.6)	(8.7)	(14.6)	(7.1)
Hirneiss 2009[15]	43	Normal working population	68.6	79.1	75.1	90.2	90.6	96.8	85.3	89.7	97.9	88.4	97.3	92.5	88.8
n=108		- With ocular disease	(20.7)	(15.9)	(19.2)	(13.6)	(10.7)	(12.3)	(12.5)	(15.6)	(5.8)	(10.4)	(11.6)	(16.7)	(8.3)
Hoeksema 2014[7]	58 ± 17	Herpetic anterior uveitis	59.0	76.1	73.3	87.7	92.6	97.1	84.9	84.0	97.7	87.1	97.1	91.2	88.1
n=36			(19.0)	(9.3)	(22.8)	(16.7)	(12.6)	(8.1)	(14.4)	(21.9)	(7.1)	(16.2)	(10.1)	(20.3)	(10.6)
Qian 2011[4]	41	Noninfectious ocular	60.3	72.8	73.9	79.2	78.8	89.9	70.8	74.2	84.9	77.4	94.9	81.3	79.7
n=104		inflammatory disease	-	-	-	-	-	-	-	-	-	-	-	-	-
Naik 2013[5]	-	Noninfectious intermediate and posterior uveitis (Snellen VA ≥ 0.5)	59.1	70.3	76.5	78.9	80.5	87.8	71.2	75.3	86.7	81.2	92.8	83.4	80.3
n=123			-	-	-	-	-	-	-	-	-	-	-	-	-
Kuiper 2013[6]	59.5 (median)	Birdshot chorioretinopathy	61.6	63.8	75.1	68.6	70.3	84.5	71.2	64.5	84.2	66.8	80.2	67.6	71.0
n=105			-	-	-	-	-	-	-	-	-	-	-	-	-
Cahill 2005[14]	76.4 ± 5.6	Bilateral severe AMD	-	31.4	81.8	29.4	38.8	58.4	34.1	38.2	42.7	16.1	67.5	66.8	-
n=70			-	(15.8)	(20.3)	(18.6)	(24.7)	(28.1)	(25.1)	(27.1)	(29.7)	(31.3)	(27.7)	(25.1)	-

NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25. GH: General Health, GV: General Vision, OP: Ocular Pain, NA: Near Activities, DA: Distance Activities, VSSF: Vision Specific Social Functioning, VSMH: Vision Specific Mental Health, VSRD: Vision Specific Role Difficulties, VSD: Vision Specific Dependency, D: Driving, CV: Color Vision, PV: Peripheral Vision, OCS: Overall Composite Score, VA: visual acuity. AMD: age-related macular degeneration.

* Average of vision-targeted subscale scores, without GH.

that 28/104 (27%) of patients with non-infectious ocular inflammatory disease (including severe posterior and panuveitis patients) screened positive for depression. They observed that these patients scored far lower on the NEI VFQ-25 OCS than non-depressed patients. In their study, inadequate emotional support was highly associated with the development of depression.[4] In our study, depression (BDI-II score) was positively correlated with a deficiency in desired social support (SSL-D score).

The main shortcoming of our study is its modest sample size. Our sample size is considered adequate for overall analyses[23], but it may be too limited for all subgroup analyses, resulting in an underreporting of possibly relevant associations. Also, only 50% of the HLA-B27 associated AU patients participated in the present study. Between participants and non-participants we found that participants were slightly older and had a longer follow-up time, there were no other significant differences, we consider the risk of a selection bias to be small. Furthermore, our patients were seen at a tertiary referral center and therefore this population may not represent the general uveitis population.

In conclusion, patients with HLA-B27 associated AU have a relatively high VR-QOL. However, the presence of a systemic disease is associated with considerably lower VR-QOL scores and general health scores and may be associated with an increased risk of depression. In addition, depression itself is associated with a lower VR-QOL.

ACKNOWLEDGMENTS

None

REFERENCES

1. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, et al. Uveitis subtypes in a German interdisciplinary uveitis center—analysis of 1916 patients. J Rheumatol. 2009;36:127–136.
2. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 2005;50:364-388.
3. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol. 2001;119:841-849.
4. Qian Y, Glaser T, Esterberg E, Acharya NR. Depression and visual functioning in patients with ocular inflammatory disease. Am J Ophthalmol. 2012;153:370-378.
5. Naik RK, Gries KS, Rentz AM, Kowalski JW, Revicki DA. Psychometric evaluation of he ational Eye Institute Visual Function Questionnaire and Visual FunctionQuestionnaire Utility Index in patients with non-infectious intermediate and posterior uveitis. Qual Life Res. 2013;22:2801-2808.
6. Kuiper JJ, Missotten T, Baarsma SG, Rothova A. Vision-related quality of life in patients with birdshot chorioretinopathy. Acta Ophthalmol. 2013;91:e329-331.
7. Hoeksema L, Los LI. Vision-related quality of life in herpetic anterior uveitis patients. PLoS One. 2014;9:e85224.
8. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-783
9. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol. 1998;116:1496-1504.
10. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119:1050-1058.
11. Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychol. 2001;20:112-119.
12. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
13. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. Invest Ophthalmol Vis Sci. 2012;53:5722-5727.
14. Cahill MT, Banks AD, Stinnett SS, Toth CA. Vision-related quality of life in patients with bilateral severe age-related macular degeneration. Ophthalmology. 2005;112:152-158.
15. Hirneiss C, Schmid-Tannwald C, Kernt M, Kampik A, Neubauer AS. The NEI VFQ-25 vision-related quality of life and prevalence of eye disease in a working population. Graefes Arch Clin Exp Ophthalmol. 2009;248:85-92.
16. Frick KD, Drye LT, Kempen JH, Dunn JP, Holland GN, Latkany P, et al. Associations among visual acuity and vision- and health-related quality of life among patients in the multicenter uveitis steroid treatment trial. Investigative Ophthalmology & Visual Science. 2012;53:1169-1176.
17. Ovayolu N, Ovayolu O, Karadag G. Health-related quality of life in ankylosing spondylitis, fibromyalgia syndrome, and rheumatoid arthritis: a comparison with a selected sample of healthy ındividuals. Clin Rheumatol. 2011;30:655-664.
18. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis: a comparison with the general population. Ann Rheum Dis. 2004;63:1605-1610.
19. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005;53:494-501.
20. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol. 2010;149:550-561.
21. Maca SM, Schiesser AW, Sobala A, Gruber K, Pakesch G, Prause C, et al. Distress, depression and coping in HLA-B27-associated anterior uveitis with focus on gender differences. Br J Ophthalmol. 2011;95:699-704.
22. Hyphantis T, Kotsis K, Tsifetaki N, Creed F, Drosos AA, Carvalho AF, et al. The relationship between depressive symptoms, illness perceptions and quality of life in ankylosing spondylitis in comparison to rheumatoid arthritis. Clin Rheumatol. 2013;32:635-644.
23. Mangione CM. NEI-VFQ Scoring Algorithm. Version 2000. Available at: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf

7

General discussion and future perspectives

GENERAL DISCUSSION

In this chapter we will discuss the most important findings and compare them with the current literature. We will also discuss some future perspectives for the purpose of further research. This thesis focuses on two types of anterior uveitis (AU), herpetic and HLA-B27 associated AU. The most common infectious and non-infectious forms of AU. All types of uveitis differ in ocular and patient characteristics. Therefore we studied homogeneous uveitis groups on ocular characteristics, complications, visual acuity (VA) and quality of life (QOL). This will result in a better understanding of the individual prognosis and impact of the disease with the ultimate aim to contribute to a more personalized care of uveitis patients.

Ocular characteristics, complications and the visual prognosis in herpetic and HLA-B27 associated anterior uveitis

The knowledge of different ocular and patient characteristics of the various types of uveitis in different populations is important in making the diagnosis, inform the patient and to customize treatment strategies. There are a lot of differences in reported rates of ocular complications. Factors contributing to the differences include non-uniform definitions and variable follow-up times, which is a well-recognized problem in the field of uveitis.[1] That is why we conducted a study that 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 2)**.

We performed a retrospective, observational study of 62 herpetic and 113 HLA-B27 associated AU patients, seen at the ophthalmology department of the University Medical Center of Groningen. We used the guidelines for uniform reporting in uveitis studies as developed by the standardization of uveitis nomenclature (SUN) working group.[1]

The results show similarities and differences between herpetic and HLA-B27 associated AU. In herpetic AU, the most common complications are keratitis, elevated intraocular pressure (IOP), cataract, posterior synechiae and glaucoma and in HLA-B27 AU posterior synechiae, elevated IOP, cataract, cystoid macular oedema and glaucoma. The incidence rate of ocular complications overall is higher in herpetic compared to HLA-B27 associated AU, which is mainly due to higher incidence rates of glaucoma, cataract and keratitis in herpetic AU.
Rates of ocular complications given in the literature vary for both groups. For glaucoma they range from 1.8 to 30% in herpetic AU and in HLA-B27 associated AU this varies between 0 and 20%.[2-8] Also the development of cataract varies in the literature, and is reported to develop in 13 to 32% in herpetic and in 5 to 28% in HLA-B27 associated AU.[3,4,7-10] This difference in reported ocular complications seems to be caused by nonhomogeneous patient groups, non-uniform definitions, and different ways to report data.

Previous studies have often focused on large groups of heterogeneous uveitis patients. The benefit of this type of research is that this results in large numbers of patients. The disadvantage is that it says less about the different uveitis entities and the subgroups in these studies are often small, resulting in less reliable outcomes.[11-14] An exception is HLA-B27 associated anterior uveitis, wherein a reasonable amount of research, with homogeneous patient groups, has been conducted.[3,15-20] Unfortunately, these HLA-B27 positive patients were often compared with HLA-B27 negative patients, which represents a very heterogeneous group of patients of various uveitis entities.[4,10, 21-27] Additionally, these HLA-B27 negative patient groups consists for a substantial part of patients with idiopathic uveitis. During follow-up many of these idiopathic patients will be diagnosed with a specific uveitis entity. This means that it is unsure which comparison is made. To understand the individual prognosis and impact of the disease per uveitis entity, it is important to investigate larger homogeneous patient groups. In recent years more and more research is conducted in this way, for example research on herpetic anterior uveitis.[7-9,28] Eventually this will lead to the development of more individualized entity-related counseling strategies.

A second problem in the field of uveitis are non-uniform definitions. In 1987, the International Uveitis Study Group developed criteria based on the anatomical localisation of the inflammation.[29] In 2005 this was updated by the SUN working group, which developed guidelines for reporting clinical data in the field of uveitis, including the use of definitions for ocular complications.[1] Because of the lack of given definitions in the earlier guidelines (before 2005), many researchers came up with their own definitions, or did not specify the definitions used.[3,9,10,15,22,23] In addition, a lot of studies are still conducted without using guidelines for reporting clinical data, even after the SUN working group published their guidelines.[7,11,25,27,28] This use of non-uniform definitions has led to a wide variety in reported incidences of ocular complications and makes it difficult to compare studies **(see chapters 2 and 3)**. In addition, it is unsure what exactly has been investigated without specifying the used methods. Fortunately, in recent years more research is conducted with the use of the guidelines mentioned by the SUN working group**.** Most studies only use this guidelines for the classification of uveitis[16-19,24,26], others also use the guidelines for determining the definitions of ocular complications.[8,20] The use of these guidelines enables comparisons of studies in the field of uveitis. Hopefully, in the future, it will become more accepted to use these guidelines and as a consequence the variety in reported incidences of ocular complications will decline.

A third issue is the way to report data, since this can be done in different ways. The ocular complications in our study were expressed as percentages at the end of follow-up and as rate/eye-years (see **chapter 2**, *'data'*). In this way, data is corrected for variable follow-up times.[1,30] However, this method will not show when the specific complication took place in the course of the disease. If we assume that most of the complications occur in the beginning of the follow-up, a short follow-up time will lead to a higher rate/eye-years (number of events divided by the sum of less follow-up

time) and a longer follow-up time will lead to lower rate/eye-years (number of events divided by the sum of longer follow-up time). Another way of presenting data would be to give information on complications at certain time points (e.g. at 1 year follow-up, 2 year follow-up, 10 year follow-up). This would make the distribution of the complications over time more transparent.

In **chapter 2** we further found that HLA-B27 associated AU patients score better on VA at onset and during follow-up, compared to herpetic AU. In the latter, VA was lower in patients with keratitis as compared to those without. Tugal-Tutkun et al. also reported that their patients with only iridocyclitis had no permanent visual loss.[7] In addition, at ten years of follow-up, VA of herpetic AU patients without keratitis seemed to be comparable with that of HLA-B27 associated AU patients. In our study, most patients end up with a reasonably good VA at ten years follow-up. In contrast, previous studies described visual impairment in a substantial proportion of HLA-B27 associated AU patients. Except for shorter follow-up times, there is no obvious explanation for this dissimilarity.[4,10,31] In recent years, there is a development in more advanced systemic therapies (e.g. adalimumab, certolizumab and golimumab) for the prevention of uveitis flares in HLA-B27 uveitis.[32-35] The assumption is that with less uveitis flares, the VA will remain better. The efficacy and visual prognosis of these treatment options should be further investigated.

Elevated intraocular pressure and glaucoma in herpetic anterior uveitis

Because we found a high prevalence of elevated IOP and eventually secondary glaucoma in patients with herpetic AU **(chapter 2)**, we performed a study on risk factors for the development of glaucoma **(chapter 3)**. Identifying these risk factors can help to determine how therapeutic modalities can prevent glaucoma in this patient group.

We found that elevated IOP and secondary glaucoma are frequent complications of herpetic AU. In addition, we found a wide variety between studies regarding the definitions of elevated IOP and secondary glaucoma, and as a result a wide variation in reported incidences of these complications **(chapter 3)**.[5,7-9,28] This finding underlines the need for using standardized guidelines as mentioned in the discussion above.

Previous studies showed that elevated IOP is a risk factor for the development of secondary glaucoma and that specific the level of IOP and the reduced diurnal-to-nocturnal change of habitual IOP are of importance.[36-41] In our study, herpetic AU patients who developed secondary glaucoma had more often elevated IOP during follow-up and endured significantly more IOP peaks than patients without glaucoma. These IOP peaks may be prevented by early and prolonged use of antiviral and anti-glaucoma medication. In a recent review by Zandi et al. the authors also concluded that prophylactic treatment may need to be continued indefinitely, frequently in conjunction with the administration of topical corticosteroids at low doses and of anti-glaucoma agents.[42] Future studies are needed to evaluate whether this eventually prevents the development of secondary glaucoma.

Comparison of unilateral and bilateral HLA-B27 associated anterior uveitis

In HLA-B27 associated AU, the uveitis can be unilateral (always the same eye) or bilateral (simultaneous or alternating), it would be interesting to know if these different manifestations represent the same or different disease entities. That is why we evaluated the ocular and patient characteristics of these two patient groups **(chapter 4)**.

We found that unilateral and bilateral HLA-B27 associated AU are generally comparable. They differ in age at the onset of uveitis and the presence of an associated systemic disease. In addition, HLA-B27 AU is more frequently seen in men, it is mainly bilaterally alternating, and more than half of the patients have signs of a severe inflammation, such as anterior chamber fibrin and posterior synechiae.

Bilateral patients were younger than unilateral patients (31 versus 37 years). Unfortunately, a direct comparison with other studies is not possible, because we could not find any information on differences in age at onset between unilateral and bilateral patients in the literature. Patients with bilateral AU more often had an associated systemic disease as compared to patients with unilateral AU (62% versus 37%). In the literature there is no significant difference found between unilateral and bilateral patients, however these studies are not primarily designed to examine the difference of unilateral and bilateral patients.[4,24] Knowing that bilateral patients are more at risk for developing an associated systemic disease, can be useful in the clinical setting. It may be worth considering to refer these patients sooner to a rheumatologist for a systemic evaluation, especially if they have systemic complaints.

In most patients the AU begins unilaterally and becomes bilateral during follow-up. In our study, the median interval between uveitis in the first and second eye was 4.2 years. The total follow up of the unilateral patients was 2.7 years. This indicates that it could well be that the second eye of seemingly unilateral patients will get involved in the future. In the literature the prevalence of bilateral disease varies from 27 to 52%, the follow up in these studies varied between 1.2 and 5.2 years.[3,4,10,18,19,21,25] The relatively short follow-up in the performed studies indicate that probably the percentage of bilateral patients will eventually be even higher if the follow-up is longer.

Our study shows that unilateral and bilateral patients both have a good prognosis with regard to VA and the development of ocular complications. Also the VA at the end of follow-up did not differ between the first and second affected eye in bilateral patients. Altogether, because unilateral and bilateral HLA-B27 associated AU are generally comparable with regard to ocular complications, course of the disease, VA, and treatment, they represent probably the same disease entity.

Vision related quality of life in anterior uveitis

Awareness of the ocular and patient characteristics of the different uveitis entities is important in making the right diagnosis and to start the appropriate treatment, trying to prevent ocular complications and support a better VA outcome. A better VA in the long run and less ocular complications should eventually result in a better QOL. In recent years there is more and more interest in the QOL of patients, not only by clinicians, but also by the patient and patient associations. QOL is defined as a state of complete physical, mental and social well-being.[43] Outcomes of QOL questionnaires give information on the impact of the disease on the patient's daily life. This is why we evaluated the vision related quality of life (VR-QOL) in herpetic and HLA-B27 associated AU patients **(chapters 5 and 6)**.

Schiffman et al. found already in 2001 that uveitis patients have a poorer visual functioning and a lower general health status compared to healthy subjects.[44] A recent study by Shamdas et al. showed that poor vision in the better seeing eye, bilateral disease and concurrent glaucomatous optic neuropathy were predictors of poor QOL in uveitis patients.[45] In addition, Verhagen et al. found in patients with non-infectious uveitis that ocular pain also has an impact on QOL.[46] In recent years there is more research conducted into specific uveitis entities. These studies 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.[47-49]

Vision related quality of life in herpetic anterior uveitis

Previous research focuses mainly on non-infectious uveitis or nonhomogeneous uveitis groups.[44,45,46,50-52] Research on QOL in infectious uveitis is scarce. As far as we know, there is no information available in the literature on QOL in a homogeneous herpetic AU group. For this reason we examined the VR-QOL and the prevalence and severity of depression in herpetic AU **(chapter 5)**.

We found that VR-QOL is reasonably high in herpetic AU patients. Generally herpetic AU patients score almost the same as those in the working population and in acute posterior vitreous detachment patients.[53,54] A possible explanation for a better QOL in our patient group, despite the relatively high percentage of patients with glaucoma and keratitis **(chapter 2 and 3)**, is that all our patients had a unilateral disease. These patients generally have no complaints and a good VA in the unaffected eye.

We also looked at the prevalence and severity of depression. A worse depression score (BDI-II) was correlated with a worse VR-QOL (NEI-VFQ-25). However depression itself was scarce in our study group, with only one patient having a moderate depression. Onal et al. showed that a positive screening test for depression and anxiety is common in patients with uveitis. In this study low vision and panuveitis are associated with depression and depression is associated with impairment of VR-QOL.[55] Our study shows that depression is less common in AU with a relatively

good visual prognosis. The relatively good VR-QOL and low number of patients with depression, indicate that these patients do not need specific screening and intervention measures on QOL and depression.

Vision related quality of life in HLA-B27 associated anterior uveitis

Because we were interested if patients with HLA-B27 associated AU differ with regard to VR-QOL compared to herpetic AU patients in the same region, we evaluated this in **chapter 6**. Patients with HLA-B27 associated AU have a relatively high VR-QOL, scoring almost the same as those in the working population.[53] In addition, they also score comparable to herpetic AU patients **(chapter 5)**.

The difference that we found, is that HLA-B27 associated AU patients score lower on general health. In addition, patients with an associated systemic disease scored even lower on general health, compared to patients without an associated systemic disease. In the literature we found several studies on health related QOL in ankylosing spondylitis patients. These studies also found an evident influence of systemic disease on reported physical and mental health.[56-58]

There were six patients with a mild depression in patients with HLA-B27 associated AU, compared to one in herpetic AU patients (10 versus 3%). Patients with a depression also scored lower on VR-QOL and more often had ankylosing spondylitis (5/6 (83%)). This suggests that a systemic disease increases the chance of developing a depression. Qian et al. also observed that non-infectious uveitis patients with a depression scored far lower on VR-QOL, than non-depressed patients, however this study also included severe posterior and panuveitis patients.[59]

Overall, it seems that infectious and non-infectious AU patients have a relatively high VR-QOL. But awareness on lowered general health and depression, especially in patients with an associated systemic disease, is crucial.

FUTURE PERSPECTIVES

The research conducted in this thesis adds new information to the already existing literature. We used homogeneous patient groups and the guidelines for uniform reporting in uveitis studies as developed by the SUN working group.[1] To be able to compare future studies, it is important to use a guideline for reporting data. This should for example prevent a wide variety of definitions of ocular complications between studies, hopefully leading to a less wide variety of reported incidences of these complications. In addition, the use of homogeneous patient groups is also important to compare future studies and to contribute to a more personalized care of uveitis patients.

Most studies performed in the literature are retrospective studies, just like the research that we conducted. To answer certain issues, prospective studies are needed. It would be interesting to try to tie the ocular complications to the disease process or the side effects of the uveitis treatment (e.g. steroid use). Since therapy and the disease process are entwined, this cannot reliably be done in a retrospective study. In addition, **chapter 3** gives an indication that IOP peaks may be prevented by early and prolonged use of antiviral and anti-glaucoma medication. A prospective study is needed to determine the optimum starting point and duration of treatment and to evaluate whether this eventually prevents the development of secondary glaucoma.

Further, it would be interesting to know the chance for unilateral HLA-B27 associated AU patients to become bilateral. In our study **(chapter 4)** the median interval between uveitis in the first and second eye was 4.2 years and the total follow up of the unilateral patients was 2.7 years. This means that it could well be that the second eye of seemingly unilateral patients will get involved in the future. A longer (prospective) study is needed to provide clarity on this matter.

Patients often want to know the risk of recurrence of the uveitis and the factors that trigger a relapse. To answer these questions, factors that could lead to a uveitis should be investigated (e.g. stress, other diseases, season, compromised immune system) in a prospective way, at the time of the active uveitis. At this moment we cannot give an answer on this matter.

With regard to the QOL studies **(chapter 5 and 6)**, both studies have a modest sample size. The sample size is considered adequate for overall analyses, but it may be too limited for all subgroup analyses. Further studies with larger patient groups are needed to investigate if there are additional associations. A possibility to obtain more patients is conducting a multicenter study.

Recent research emphasizes that the definitive diagnosis of herpetic AU can only be proven by aqueous humor analysis.[60,61] Because the research we conducted is mainly retrospective, most of the herpetic patients we included were diagnosed by clinical characteristics for HSV or VZV, including unilateral AU, small or medium sized **keratic precipitates**, iris atrophy, elevated IOP at onset, keratitis and skin lesions. In recent years more aqueous humor analyses are performed, which allows for future (prospective) studies to include more patients who are proven herpetic.

REFERENCES

1. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
2. Rothova A, Buitenhuis HJ, Christiaans BJ, et al. Acute anterior uveitis (AAU) and HLA-B27. Br J Rheumatol. 1983;22:144-145.
3. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. Am J Ophthalmol. 1996;121:47-56.
4. Power WJ, Rodriguez A, Pedroza-Seres M, et al. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998;105:1646-1651.
5. Takahashi T, Ohtani S, Miyata K, et al. A clinical evaluation of uveitis-associated secondary glaucoma. Jpn J Ophthalmol. 2002;46:556-562.
6. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 2005;50:364-388.
7. Tugal-Tutkun I, Otük-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: a retrospective study of 111 cases. Int Ophthalmol. 2010;30:559-565.
8. Wensing B, Relvas LM, Caspers LE, et al. Comparison of rubella virus- and herpes virus-associated anterior uveitis: clinical manifestations and visual prognosis. Ophthalmology. 2011;118:1905-1910.
9. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis: a clinical evaluation and comparison. Ophthalmology. 2002;109:1532-1537.
10. Tuncer S, Adam YS, Urgancioglu M, et al. Clinical features and outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis in a Turkish patient population. Ocul Immunol Inflamm. 2005;13:367-373.
11. Carrim ZI, Ahmed TY, Taguri AH. The relationship between stress and acute anterior uveitis. Acta Ophthalmol Scand. 2006;84:795-798.
12. Barisani-Asenbauer T, Maca SM, Mejdoubi L, Emminger W, Machold K, Auer H. Uveitis- a rare disease often associated with systemic diseases and infections- a systematic review of 2619 patients. Orphanet J Rare Dis. 2012;7:57.
13. Al-Mezaine HS, Kangave D, Abu El-Asrar AM. Patterns of uveitis in patients admitted to a University Hospital in Riyadh, Saudi Arabia. Ocul Immunol Inflamm. 2010;18:424-431.
14. Sabhapandit S, Murthy SI, Singh VM, et al. Epidemiology and Clinical Features of Uveitis from Urban Populations in South India. Ocul Immunol Inflamm. 2017;25:S39-S45.
15. Monnet D, Breban M, Hudry C, Dougados M, Brézin AP. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. Ophthalmology. 2004;111:802-809.
16. Braakenburg AM, de Valk HW, de Boer J, Rothova A. Human leukocyte antigen-B27-associated uveitis: long-term follow-up and gender differences. Am J Ophthalmol. 2008;145:472-479.
17. Agnani S, Choi D, Martin TM, et al. Gender and laterality affect recurrences of acute anterior uveitis. Br J Ophthalmol. 2010;94:1643-1647.
18. Loh AR, Acharya NR. Incidence rates and risk factors for ocular complications and vision loss in HLA-B27-associated uveitis. Am J Ophthalmol. 2010;150:534-542.
19. Wang YQ, Lu XY, Wang YL, et al. Clinical analysis of 240 patients with HLA-B27 associated acute anterior uveitis. Eye Sci. 2012;27:169-172.
20. Verhagen FH, Brouwer AH, Kuiper JJ, Ossewaarde-van Norel J, Ten Dam-van Loon NH, de Boer JH. Potential Predictors of Poor Visual Outcome in Human Leukocyte Antigen-B27-Associated Uveitis. Am J Ophthalmol. 2016;165:179-187.
21. Rothova A, van Veenedaal WG, Linssen A, Glasius E, Kijlstra A, de Jong PT. Clinical features of acute anterior uveitis. Am J Ophthalmol. 1987;103:137-145.
22. Wakefield D, Montanaro A, McCluskey P. Acute anterior uveitis and HLA-B27. Surv Ophthalmol. 1991;36:223–232.
23. Linssen A, Meenken C. Outcomes of HLA-B27-positive and HLA-B27-negative acute anterior uveitis. Am J Ophthalmol. 1995;120:351-361.
24. Park SC, Ham DI. Clinical features and prognosis of HLA-B27 positive and negative anterior uveitis in a Korean population. J Korean Med Sci. 2009;24:722-728.
25. Accorinti M, Iannetti L, Liverani M, Caggiano C, Gilardi M. Clinical features and prognosis of HLA B27-associated acute anterior uveitis in an Italian patient population. Ocul Immunol Inflamm. 2010;18:91-96.
26. Karaconji T, Maconochie Z, McCluskey P. Acute anterior uveitis in Sydney. Ocul Immunol Inflamm. 2013;21:108-114.
27. Torres S, Borges S, Artiles A. HLA B27 and clinical features of acute anterior uveitis in Cuba. Ocul Immunol Inflamm. 2013;21:119-123.
28. Sungur GK, Hazirolan D, Yalvac IS, Ozer PA, Aslan BS, Duman S. Incidence and prognosis of ocular hypertension secondary to viral uveitis. Int Ophthalmol. 2010;30:191-194.

29. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. Am J Ophthalmol 1987;103:234–235.
30. Jabs DA. Improving the reporting of clinical case series. Am J Ophthalmol. 2005;139:900-905.
31. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, et al. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332-336.
32. Jaffe GJ, Dick AD, Brezin AP, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med 2016;375:932–943.
33. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive noninfectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet 2016; 388:1183–1192.
34. Rudwaleit M, Rosenbaum JT, Landewe R, et al. Observed incidence of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. Arthritis Care Res 2016;68:838–844.
35. Yazgan S, Celik U, Isik M, et al. Efficacy of golimumab on recurrent uveitis in HLA-B27-positive ankylosing spondylitis. Int Ophthalmol 2016;37:139–145.
36. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol. 1991;109:1090-1095.
37. Varma R, Hilton SC, Tielsch JM, Katz J, Quigley HA, Sommer A. Neural rim area declines with increased intraocular pressure in urban Americans. Arch Ophthalmol. 1995;113:1001-1005.
38. Healey PR, Mitchell P, Smith W, Wang JJ. The influence of age and intraocular pressure on the optic cup in a normal population. J Glaucoma. 1997;6:274-278.
39. Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci. 2000;41:40-48.
40. Liu JH, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003;44:1586-1590.
41. Boland MV, Quigley HA. Risk factors and open-angle glaucoma: classification and application. J Glaucoma. 2007;16:406-418.
42. Zandi S, Bodaghi B, Garweg JG. Review for Disease of the Year: Treatment of Viral Anterior Uveitis: A Perspective. Ocul Immunol Inflamm. 2018;26:1135-1142.
43. World Health Organization: The constitution of the World Health Organization. WHO Chron. 1947;1:29.
44. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol. 2001;119:841-849.
45. Shamdas M, Bassilious K, Murray PI. Health-related quality of life in patients with uveitis. Br J Ophthalmol. 2018 [Epub ahead of print]
46. Verhagen FH, Wijnhoven R, Ossewaarde-van Norel J, et al. Prevalence and characteristics of ocular pain in non-infectious uveitis: a quality of life study. Br J Ophthalmol. 2018;102:1160-1166.
47. Kuiper JJ, Missotten T, Baarsma SG, Rothova A. Vision-related quality of life in patients with birdshot chorioretinopathy. Acta Ophthalmol. 2013;91:e329-331.
48. Fabiani C, Vitale A, Orlando I, et al. Quality of life impairment in Behçet›s disease and relationship with disease activity: a prospective study. Intern Emerg Med. 2017;12:947-955.
49. Haasnoot AJW, Sint Jago NFM, Tekstra J, de Boer JH. Impact of Uveitis on Quality of Life in Adult Patients With Juvenile Idiopathic Arthritis. Arthritis Care Res. 2017;69:1895-1902.
50. Tan P, Koh YT, Wong PY, Teoh SC. Evaluation of the impact of uveitis on visual-related quality of life. Ocul Immunol Inflamm. 2012;20:453-459.
51. Hui MM, Wakefield D, Patel I, Cvejic E, McCluskey PJ, Chang JH. Visual Functioning and Health-related Quality-of-Life are Compromised in Patients with Uveitis. Ocul Immunol Inflamm. 2017;25:486-491.
52. Arriola-Villalobos P, Abásolo L, García-Feijoo J, et al. Vision-related Quality of Life in Patients with Non-infectious Uveitis: A Cross-sectional Study. Ocul Immunol Inflamm. 2018;26:717-725.
53 Hirneiss C, Schmid-Tannwald C, Kernt M, Kampik A, Neubauer AS. The NEI VFQ-25 vision-related quality of life and prevalence of eye disease in a working population. Graefes Arch Clin Exp Ophthalmol 2010;248:85-92.
54. Schweitzer KD, Eneh AA, Hurst J, et al. Visual function analysis in acute posterior vitreous detachment. Can J Ophthalmol 2011;46:232-236.
55. Onal S, Oray M, Yasa C, et al. Screening for Depression and Anxiety in Patients with Active Uveitis. Ocul Immunol Inflamm. 2018;26:1078-1093.
56. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis: a comparison with the general population. Ann Rheum Dis. 2004;63:1605-1610.
57. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005;53:494-501.

58. Ovayolu N, Ovayolu O, Karadag G. Health-related quality of life in ankylosing spondylitis, fibromyalgia syndrome, and rheumatoid arthritis: a comparison with a selected sample of healthy ındividuals. Clin Rheumatol. 2011;30:655-664.
59. Qian Y, Glaser T, Esterberg E, Acharya NR. Depression and visual functioning in patients with ocular inflammatory disease. Am J Ophthalmol. 2012;153:370-378.
60. Groen-Hakan F, Babu K, Tugal-Tutkun I, et al. Challenges of Diagnosing Viral Anterior Uveitis. Ocul Immunol Inflamm. 2017;25:710-720.
61. Wensing B, Mochizuki M, De Boer JH. Clinical Characteristics of Herpes Simplex Virus Associated Anterior Uveitis. Ocul Immunol Inflamm. 2018;26:333-337.

8

Summary

SUMMARY

Uveitis an important cause of blindness and visual impairment. The ocular characteristics, complications and visual acuity (VA) during follow-up differ for the different uveitis entities. The burden of anterior uveitis (AU) can be measured by determining the vision related quality of life (VR-QOL) and is an important measuring tool. We believe that it is important to investigate homogeneous uveitis groups to contribute to a more personalized care of uveitis patients. In addition, using the guidelines for uniform reporting in uveitis as developed by the standardization of uveitis nomenclature (SUN) working group, will enable comparisons with future studies in the field. This thesis discusses two types of anterior uveitis, HLA-B27 associated AU, the most common non-infectious form, and herpetic AU, the most common infectious form.

In **chapter 1** we provide an introduction to this thesis and give information about the aims of the studies we conducted. **Chapter 2** gives information on the rate of complications, ocular characteristics and the visual prognosis in herpetic (HSV and VZV) AU compared to HLA-B27 associated AU. We found a worse visual prognosis in herpetic versus HLA-B27 associated AU, which is probably related to a higher prevalence of corneal scarring and glaucoma in the former. In addition, herpetic AU patients have more ocular complications overall. This information may be helpful in developing individualized entity-related counseling strategies.

In **chapter 3** we describe the incidence of elevated intraocular pressure (IOP) and secondary glaucoma in herpetic (HSV and VZV) AU. We found that elevated IOP and secondary glaucoma are frequent complications of viral AU. In addition, we found a wide variety between studies regarding the definitions of elevated IOP and secondary glaucoma, and as a result a wide variation in reported incidences of these complications. This underlines the need for standardized criteria such as developed by the SUN working group.

We evaluated whether ocular and patient characteristics differ between unilateral (always the same eye) or bilateral (simultaneous or alternating) HLA-B27 associated AU with or without systemic disease in **chapter 4**. We found that unilateral and bilateral HLA-B27 associated AU are generally comparable, which indicates that it is probably the same disease entity. This study shows that unilateral and bilateral patients both have a good prognosis with regard to VA and the development of ocular complications. In addition, bilateral AU patients more often had an associated systemic disease.

In **chapter 5** we report on the VR-QOL and the prevalence and severity of depression in herpetic (HSV and VZV) AU. Herpetic AU affects the VR-QOL, but only in a moderate way. The prevalence of depression in our group of herpetic AU patients was low and therefore does not seem to indicate a need for specific screening and intervention measures in this specific patient group.

In **chapter 6** we evaluate the VR-QOL in a group of patients with HLA-B27 associated AU. Patients with HLA-B27 associated AU have a relatively high VR-QOL. However, the presence of a systemic disease is associated with considerably lower VR-QOL and general health scores and may be associated with an increased risk of depression. In addition, depression itself is associated with a lower VR-QOL.

In **chapter 7** the most important findings are discussed and ideas for future research are given.

9

Samenvatting

SAMENVATTING

Uveïtis is een belangrijke oorzaak van blindheid en slechtziendheid. De oculaire kenmerken, complicaties en visus gedurende follow-up, verschillen per verschillende uveïtis entiteiten. De last van uveïtis anterior (UA) kan gemeten worden door het bepalen van de visus gerelateerde kwaliteit van leven, dit is een belangrijk meetinstrument. Wij zijn van mening dat het belangrijk is om homogene uveïtis groepen te onderzoeken, om zo bij te dragen aan het ontwikkelen van een meer geïndividualiseerde zorg voor patiënten met uveïtis. Daarnaast zal het gebruiken van de richtlijn voor uniforme rapportage bij uveïtis, zoals ontwikkeld door de standaardisatie van de uveïtis nomenclatuur (SUN) werkgroep, het mogelijk maken om toekomstige studies op het gebied van uveïtis te vergelijken. In dit proefschrift zullen twee soorten UA besproken worden, HLA-B27 geassocieerde UA, de meest voorkomende non-infectieuze vorm, en herpetische UA, de meest voorkomende infectieuze vorm.

In **hoofdstuk 1** van dit proefschrift geven we een introductie en informatie over de doelstellingen van de verrichte studies. **Hoofdstuk 2** geeft informatie over hoe vaak oculaire complicaties voorkomen, kenmerken en visuele prognose bij herpetische (HSV en VZV) UA vergeleken met HLA-B27 geassocieerde UA. We vonden een slechtere visuele prognose bij herpetische UA, vergeleken met HLA-B27 geassocieerde UA. Dit heeft vermoedelijk een relatie met de hogere prevalentie van cornea littekens en glaucoom in de herpetische groep. Daarnaast hebben herpetische UA patiënten over het algemeen meer oculaire complicaties. Deze informatie kan nuttig zijn bij het ontwikkelen van een meer geïndividualiseerde zorg per uveïtis entiteit.

In **hoofdstuk 3** beschrijven we de incidentie van verhoogde oogdruk en secundair glaucoom in herpetische (HSV en VZV) UA. We vonden dat verhoogde oogdruk en secundair glaucoom veel voorkomende complicaties zijn van virale UA. Daarnaast vonden we een grote variatie wat betreft definities van verhoogde oogdruk en secundair glaucoom, met als resultaat een grote variatie aan gerapporteerde incidenties van deze complicaties. Dit benadrukt de behoefte aan gestandaardiseerde criteria zoals ontwikkeld door de SUN werkgroep.

We hebben in **hoofdstuk 4** vergeleken of oculaire en patiënt kenmerken verschillen tussen unilaterale (altijd hetzelfde oog) of bilaterale (tegelijkertijd of alternerend) HLA-B27 geassocieerde UA, met of zonder systeemziekte. We hebben gevonden dat unilaterale en bilaterale HLA-B27 geassocieerde UA over het algemeen vergelijkbaar zijn, wat er op wijst dat dit waarschijnlijk dezelfde ziekte entiteit is. Uit deze studie blijkt dat unilaterale en bilaterale patiënten beide een goede prognose hebben wat betreft visus en het ontwikkelen van oculaire complicaties. Daarnaast hebben bilaterale UA patiënten vaker een geassocieerde systeemziekte.

In **hoofdstuk 5** beschrijven we de visus gerelateerde kwaliteit van leven en de prevalentie en ernst van depressie in herpetische (HSV en VZV) UA. Herpetische UA heeft invloed op de visus

gerelateerde kwaliteit van leven, maar die invloed is zeer gering. De prevalentie van depressie in onze groep herpetische UA patiënten was laag en daarom lijkt er geen indicatie voor speciale screening en interventie-maatregelen in deze specifieke patiënten groep.

We hebben de visus gerelateerde kwaliteit van leven onderzocht in een patiënten groep met HLA-B27 geassocieerde UA in **hoofdstuk 6**. Patiënten met HLA-B27 geassocieerde UA hebben een relatief hoge visus gerelateerde kwaliteit van leven. Echter, het hebben van een systeemziekte is geassocieerd met een aanzienlijke lagere algemene gezondheidsscore en is mogelijk geassocieerd met een verhoogde kans op depressie. Daarnaast is het hebben van een depressie geassocieerd met een lagere visus gerelateerde kwaliteit van leven.

In **hoofdstuk 7** worden de belangrijkste bevindingen besproken en ideeën voor verder onderzoek worden benoemd.

10

Appendices

Dankwoord
Bibliography
About the author
Questionnaires (NEI-VFQ-25, BDI-II, SSL-I/SSL-D)

DANKWOORD

Het heeft even geduurd, maar het is uiteindelijk toch gelukt om dit proefschrift af te ronden. Natuurlijk was dit niet gelukt zonder de inspanningen en inbreng van anderen. Iedereen die op welke manier dan ook een bijdrage heeft geleverd wil ik graag bedanken. Daarnaast wil ik hieronder nog een aantal mensen in het bijzonder bedanken.

Dr. L.I. Los. Allereerst wil ik mijn co-promotor, Leonie, bedanken. Al voordat het eigenlijke promotietraject tot stand kwam, was jij al mijn begeleider van het wetenschappelijk onderzoek vanuit de studie geneeskunde. Hierna heb jij mij enthousiast gemaakt voor het doen van onderzoek en hebben we nog vele jaren samen aan dit uiteindelijke project gewerkt. Ik heb de samenwerking altijd als zeer prettig ervaren. Je gaf me veel ruimte om me te ontwikkelen als onderzoeker en de overlegmomenten die we hadden verliepen altijd goed en heb ik als gezellige en leerzame momenten ervaren. Dus bedankt voor de goede begeleiding al deze jaren.

Prof. dr. J.M.M. Hooymans. Ook wil ik graag mijn promotor, prof. dr. J.M.M. Hooymans, bedanken. Beste Anneke, samen met Leonie heb jij al deze jaren het toezicht gehouden op het promotietraject. Dit deed je altijd met veel interesse en enthousiasme. De voortgangsgesprekken gaven vaak nieuwe inzichten en zorgden er voor dat we op het juiste pad bleven. Bedankt voor de begeleiding en het duidelijke vertrouwen dat het uiteindelijke doel bereikt zou worden.

Prof. dr. N.M. Jansonius. Beste Nomdo, bedankt voor al je hulp tijdens het onderzoek. Je hebt een bijzonder scherpe blik, waardoor je vaak met adviezen kwam die leiden tot extra analyses en verbeteringen, uiteindelijk werden de artikelen er altijd sterker van. Met name je bijzonder uitgebreide kennis van statistiek heeft ons vaak verder geholpen. Daarnaast waardeer ik het dat je als afdelingshoofd altijd het belang benadrukt van wetenschappelijk onderzoek en mij ook de ruimte bood om mij daar verder in te ontwikkelen.

Leden van de beoordelingscommissie. Beste Prof. dr. H. Bootsma, Prof. dr. A. Rothova en Prof. dr. J. de Boer, bedankt voor het vrijmaken van de tijd om dit proefschrift te lezen en te beoordelen.

Wietse Wieringa. Wij zijn lang collega's geweest op het LEO en de laatste jaren zaten we ook nog gezellig naast elkaar. Ik ben je gaan beschouwen als een zeer fijne collega en goede vriend en ik ben er ook erg blij mee dat je mijn paranimf wil zijn. Doordat onze onderzoeken veel raakvlakken hebben, was het altijd fijn te kunnen overleggen, adviezen te kunnen uitwisselen en een luisterend oor te hebben. We bezochten samen (met Leonie) het IOIS congres in Valencia, een ervaring om niet te vergeten. Zo terugkijkend hebben we toch veel meegemaakt en ik kijk hier tevreden op terug. Bedankt voor deze mooie tijd.

Annet van der Meer. Annet wij hebben elkaar leren kennen op de middelbare school, de vijfde klas van het atheneum op het Fivelcollege te Delfzijl, in 2002. Ik had net de HAVO afgerond en twijfelde nog welke richting ik verder op zou gaan, dus koos ik voor eerst nog twee jaren atheneum. Maar goed ook, anders had ik jou nooit leren kennen. We hebben een mooie tijd gehad op de middelbare school, met veel stappen en Within temptation bezoeken. Jij weet als geen ander dat het leven niet altijd even makkelijk is en ik waardeer het enorm dat je ondanks alles altijd voor anderen klaar staat. Ik vind het ontzettend fijn dat je mijn paranimf wil zijn.

Secretariaat oogheelkunde. Ella, Stella, Fenna en Diana, bedankt voor jullie assistentie bij de praktische zaken en luisterend oor. Zonder jullie kennis van zaken zou het onderzoek nog veel meer tijd hebben gekost. Fenna jij ook bedankt voor het opzoeken van de vele moeilijk verkrijgbare artikelen, het lukte je elke keer weer. Daarnaast heb ik erg genoten van alle roddels en nieuwtjes die we op vrijdagmiddag bespraken.

Joke van Enk, Luuk Mooibroek, Wim Berghuis en Wim Nieuwold, bedankt voor alle hulp die nodig was tijdens mijn promotieonderzoek.

Onderzoekers LEO. Door de jaren heen zijn er nogal wat collega's voorbij gekomen: Else, Wietse, Michael, Shao Chong, Esther, Francisco, Margriet, Christiaan, Doety, Lisanne, Tim, Nancy, Bernadette, Ronald, Bart, Marleen, Casper, Thom, Wouter, Esra, Inge, Lukas, Ruth. Het was altijd gezellig op het LEO en zelfs de herinnering aan de zwaluwspuugkoekjes en de gezoute gedroogde pruimen van Shao Chong geven een warm gevoel. Terugkijkend heb ik ontzettend veel mensen leren kennen op het LEO en heb ik er altijd met veel plezier gewerkt. Bedankt allemaal voor deze mooie tijd.

Coördinatoren / management polikliniek oogheelkunde UMCG. Janneke, Ruben en Rogier, bedankt voor het mogelijk maken dat ik de tijd heb gekregen om tijdens mijn opleiding als AIOS oogheelkunde mijn onderzoek af te ronden.

MMA afdeling oogheelkunde UMCG. Tijdens mijn onderzoek heb ik misschien wel honderden medische dossiers opgevraagd. Bedankt dat jullie deze altijd zorgvuldig voor mij bewaarden.

Collega AIOS oogheelkunde UMCG. Bedankt dat jullie mij de ruimte gaven om mijn promotietraject af te ronden tijdens de opleiding. Er was altijd veel interesse in het onderzoek en vertrouwen dat het tot een goed einde zou komen, dank hiervoor. En misschien niet minder belangrijk, bedankt voor de goede sfeer en gezelligheid.

Stafleden oogheelkunde UMCG. Dank voor de interesse in mijn onderzoek door de jaren heen, dit werd zeer gewaardeerd.

Alle overige medewerkers afdeling oogheelkunde UMCG. Iedereen die werkzaam is op de afdeling oogheelkunde, bedankt voor alle getoonde interesse en de prettige samenwerking door de jaren heen.

Patiënten die deelnamen aan de studies. Zonder deelname van patiënten en de informatie die uit alle medische dossiers is gehaald, zou dit proefschrift geen vorm hebben gekregen. Bedankt voor jullie belangeloze inzet en de bereidheid om mee te werken aan de onderzoeken. We hopen dat de informatie die we hebben vergaard, uiteindelijk zal leiden tot beter inzicht in de ziektebeelden en uiteindelijk ook zal leiden tot een betere behandeling voor iedere individuele patiënt.

Familie en vrienden. Bedankt voor jullie interesse in mijn onderzoek. Al is het soms wat lastig om uit te leggen waar ik al die jaren nou al onderzoek naar doe, jullie blijven altijd geïnteresseerd en waarderen waar ik mee bezig ben. Ik hoop dat jullie, nu het proefschrift eindelijk daar is, iets meer inzicht krijgen in mijn werkzaamheden.

Ouders. Mam bedankt voor alle steun door de jaren heen. Ik weet dat je ontzettend trots bent op wat ik heb bereikt en dat laat je vaak genoeg blijken. Je hebt me altijd gesteund en de kansen geboden waardoor ik nu op dit punt gekomen ben. Helaas zal mijn vader dit proefschrift nooit lezen, maar ik weet dat ook hij trots zou zijn. Van kleins af aan stimuleerde hij mij altijd al om me te ontwikkelen en vooruit te komen in deze wereld. Beide ontzettend bedankt.

Jitse en Merijn. Als laatste dank aan de belangrijkste personen in mijn leven. Lieve Jitse, dank dat je altijd voor mij klaar staat en voor je onvoorwaardelijke liefde. Ik weet dat je zelf altijd een ontzettende hekel hebt gehad aan het doen van onderzoek, maar ondanks dat heb je me altijd onvoorwaardelijk gesteund. Lieve Merijn, jij bent een heerlijk lief en goedlachs kereltje, je brengt zoveel blijdschap en liefde in ons leven. Je bent mijn inspiratie voor de toekomst en we genieten elke dag van je.

BIBLIOGRAPHY

Hoeksema L, Jansonius NM, Hooymans JMM, Los LI. Unilateral versus bilateral HLA-B27 associated anterior uveitis: characteristics and visual prognosis. Submitted.

Hoeksema L, Jansonius NM, Los LI. Risk Factors for Secondary Glaucoma in Herpetic Anterior Uveitis. Am J Ophthalmol. 2017 Sep;181:55-60. Epub 2017 Jun 27.

Hoeksema L, Los LI. Vision-Related Quality of Life in Patients with Inactive HLA-B27 –Associated-Spectrum Anterior Uveitis. PLoS One. 2016 Jan 25;11(1): eCollection 2016.

Hoeksema L, Los LI. Visual Prognosis and Ocular Complications in Herpetic versus HLA-B27- or Ankylosing Spondylitis-associated Anterior Uveitis. Ocul Immunol Inflamm. 2016 Jun;24(3):302-12. Epub 2015 Jul 2.

van de Put MA, **Hoeksema L**, Wanders W, Nolte IM, Hooymans JM, Los LI. Postoperative vision-related quality of life in macula-off rhegmatogenous retinal detachment patients and its relation to visual function. PLoS One. 2014 Dec 2;9(12): eCollection 2014.

Hoeksema L, Los LI. Vision-related quality of life in herpetic anterior uveitis patients. PLoS One. 2014 Jan 2;9(1):e85224. eCollection 2014.

Compendium Geneeskunde, deel 1, de essentie van 6 jaar geneeskunde, onderdeel oogheelkunde, blz 172-198, Synopsis BV, 2016.

ABOUT THE AUTHOR

Lisette Hoeksema was born on the 20th of November 1984, in Delfzijl, the Netherlands. In 2004 she finished her secondary school, Fivelcollege in Delfzijl, and moved to Groningen. In Groningen she studied Medicine at the University of Groningen. In 2009 she started with her internships at the University Medical Center Groningen and Delfzicht hospital. In 2010 she went to the Medical Center Leeuwarden for one year of internships. The final internship and research project were conducted at the ophthalmology department of the Medical Center Groningen. The subject of the research project was oculomotor nerve pareses in herpes simplex and varicella zoster virus associated anterior uveitis, under supervision of L.I. Los, MD, PhD. In January 2012 she graduated as a Medical Doctor at the University of Groningen. After this she continued with her research project on herpetic and HLA-B27 associated anterior uveitis at the department of ophthalmology of the University Medical Center Groningen under supervision of L.I. Los, MD, PhD and prof. J.M.M. Hooymans, MD, PhD. She started with her residency in ophthalmology on June 2014 under the supervision of J.W.R. Pott, MD, PhD and prof. N.M. Jansonius, MD, PhD at the University Medical Center Groningen. Lisette is married with Jitse and in 2018 their son Merijn was born.

QUESTIONNAIRES (NEI-VFQ-25, BDI-II, SSL-I/SSL-D)

National Eye Institute
Visual Functioning Questionnaire – 25
Nederlandse Consensus Vertaling
(VFQ-25/NL)

versie 2001

VERSIE OM ZELF IN TE VULLEN (gezichtsscherpte > 0.5)

G.W. van der Sterre[1], E.S. van de Graaf[1], C.A. Verezen[2561], C.F.M. Meulendijks[3], J.S.A.G. Schouten[4], R. Saxena[1], J.R. Polling[1], L.J. van Rijn[5], C.B. Hoyng[6], M.L. Essink-Bot[7], H.J. Simonsz[1]

1 Erasmus Medisch Centrum Rotterdam, afdeling Oogheelkunde, Rotterdam
2 Ergra Low Vision consultants, Den Haag
3 Universitair Medisch Centrum St Radboud, afdeling Medical Technology Assessment, Nijmegen
4 Capgroep Epidemiologie, Universiteit Maastricht, Maastricht
5 Vrije Universiteit Medisch Centrum, afdeling Oogheelkunde, Amsterdam
6 Universitair Medisch Centrum St Radboud, afdeling Oogheelkunde, Nijmegen
7 *Erasmus Medisch Centrum Rotterdam, Instituut Maatschappelijke Gezondheidszorg, Rotterdam*

Dit is een vragenlijst met uitspraken over problemen die met uw gezichtsvermogen te maken hebben, of over gevoelens die u over uw gezichtsvermogen heeft.
Als u een bril of contactlenzen heeft, ga er dan bij de beantwoording van de vragen van uit dat u deze draagt.

Instructies:

1. In het algemeen willen we dat mensen deze vragenlijst zelf proberen in te vullen. Als u vindt dat u hulp nodig heeft, aarzel dan niet om het de projectmedewerkers te vragen, ze helpen u graag.

2. Beantwoord alstublieft alle vragen, tenzij u verzocht wordt vragen over te slaan omdat ze niet van toepassing zijn.

3. Beantwoord de vragen door het juiste cijfer te omcirkelen.

4. Als u niet zeker weet hoe een vraag te beantwoorden, geef dan het best mogelijke antwoord en maak een aantekening in de linker kantlijn.

5. Als u per ongeluk de verkeerde mogelijkheid omcirkeld heeft, dan zet u door deze cirkel een kruis en omcirkelt u het antwoord dat volgens u het juiste is.

6. Vul de vragenlijst in zonder uw antwoorden met uw vrienden of familie te bespreken.

7. De vragen hebben betrekking op uw situatie gedurende de afgelopen maand.

8. Er is een versie met grote letters voor het geval uw gezichtsvermogen tekort schiet om de lijst in te kunnen vullen.

9. Als u nog vragen heeft kunt u terecht bij leden van de staf van het project, zij zullen u graag helpen.

Verklaring van vertrouwelijkheid:

Alle informatie die identificatie mogelijk maakt van enig persoon die deze vragenlijst heeft ingevuld, zal als strikt vertrouwelijk worden beschouwd. Deze informatie zal uitsluitend worden gebruikt voor het doel van dit onderzoek, en zal niet worden onthuld of vrijgegeven voor enig ander doel, zonder voorafgaande toestemming, geopenbaard of gepubliceerd worden, uitgezonderd als vereist bij de wet.

VISUAL FUNCTIONING QUESTIONNAIRE - 25

Deel 1 – algemene gezondheid en gezichtsvermogen

1. Hoe zou u uw algehele gezondheidstoestand omschrijven:
   (omcirkel één cijfer)

Uitstekend 1
Zeer goed 2
Goed 3
Redelijk.....4
Slecht.....5

2. Zou u op dit moment zeggen dat uw gezichtsvermogen met beide ogen samen (met bril of contactlenzen, als u deze draagt), uitstekend, goed, redelijk, slecht, zeer slecht is, of bent u volledig blind?
   (omcirkel één cijfer)

Uitstekend..... .1
Goed 2
Redelijk.....3
Slecht 4
Zeer slecht 5
Volledig blind 6

3. Hoe vaak maakt u zich zorgen over uw gezichtsvermogen?
   (omcirkel één cijfer)

Nooit 1
Zelden.....2
Soms.....3
Vaak.....4
Altijd.....5

4. Hoeveel pijn of ongemak heeft u in en rond uw ogen gehad (bijvoorbeeld branderigheid, jeuk of pijn)?
   (omcirkel één cijfer)

Geen..... 1
Licht 2
Matig 3
Ernstig.....4
Heel ernstig 5

Deel 2 – moeite met het uitvoeren van activiteiten

De volgende vragen gaan over de moeite die u misschien met sommige activiteiten heeft, met bril op of contactlenzen in, mocht u die voor deze activiteit nodig hebben.

5. Hoeveel moeite heeft u om normale krantendruk te lezen?
   (omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

6. Hoeveel moeite heeft u met werkzaamheden of hobby's, waarbij u goed dichtbij moet kunnen zien, zoals koken, naaien, dingen in huis repareren, of bij het gebruik van handgereedschap?
   (omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

7. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, met het vinden van iets op een volle plank?
   (omcirkel één cijfer)

Geen enkele moeite 1
Een beetje moeite 2
Matige moeite 3
Enorme moeite 4
Hiermee gestopt vanwege het slechte gezichtsvermogen 5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

8. Hoeveel moeite heeft u met het lezen van straatnaamborden of de namen van winkels?
   (omcirkel één cijfer)

Geen enkele moeite 1
Een beetje moeite 2
Matige moeite 3
Enorme moeite 4
Hiermee gestopt vanwege het slechte gezichtsvermogen 5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

9. Hoeveel moeite kost het u, vanwege uw gezichtsvermogen, om een afstapje, een trap of een stoeprand af te stappen bij slechte verlichting of 's nachts?
   (omcirkel één cijfer)

Geen enkele moeite 1
Een beetje moeite 2
Matige moeite 3
Enorme moeite 4
Hiermee gestopt vanwege het slechte gezichtsvermogen 5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

10. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, om dingen opzij op te merken terwijl u er langs loopt?
    (omcirkel één cijfer)

Geen enkele moeite 1
Een beetje moeite 2
Matige moeite 3
Enorme moeite 4
Hiermee gestopt vanwege het slechte gezichtsvermogen 5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

11. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, om te zien hoe mensen reageren op wat u zegt?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

12. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, met het uitzoeken en combineren van uw eigen kleding?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

13. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, om bij mensen op visite te gaan, op feesten of in restaurants?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

14. Hoeveel moeite heeft u, vanwege uw gezichtsvermogen, met het uitgaan om bioscoopfilms, theater of sportevenementen te zien?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

15. Rijdt u momenteel auto, tenminste af en toe?
(omcirkel één cijfer)

Ja..... 1
Ga naar vraag 15c

Nee..... 2

15a Indien nee, heeft u nooit auto gereden of heeft u het autorijden opgegeven?
(omcirkel één cijfer)

Ik heb nooit auto gereden 1
Ga naar vraag 17

Ik heb het autorijden opgegeven 2

15b. **Als u het autorijden heeft opgegeven:** Was dat voornamelijk vanwege uw gezichtsvermogen, voornamelijk om een andere reden, of vanwege zowel uw gezichtsvermogen als om een andere reden?
(omcirkel één cijfer)

Voornamelijk mijn gezichtsvermogen 1
Ga naar vraag 17

Voornamelijk om andere redenen 2
Ga naar vraag 17

Zowel mijn gezichtsvermogen als om andere redenen..... 3
Ga naar vraag 17

15c **Als u momenteel autorijdt,** hoeveel moeite heeft u met autorijden overdag in een bekende omgeving?
(omcirkel één cijfer)

Geen enkele moeite 1
Een beetje moeite..... 2
Matige moeite 3
Enorme moeite..... 4

16. Hoeveel moeite heeft u om 's nachts auto te rijden?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

16a Hoeveel moeite heeft u met het rijden onder moeilijke omstandigheden, zoals bij slecht weer, tijdens het spitsuur, op de snelweg of in stadsverkeer?
(omcirkel één cijfer)

Geen enkele moeite.....1
Een beetje moeite.....2
Matige moeite.....3
Enorme moeite.....4
Hiermee gestopt vanwege het slechte gezichtsvermogen.....5
Hiermee gestopt om andere redenen, of op u niet van toepassing. 6

Deel 3 – omgaan met problemen met het zien

De volgende vragen gaan over hoe de dingen die u doet, beïnvloed worden door uw gezichtsvermogen. Omcirkel bij elke vraag het nummer om aan te geven of de uitspraak voor u altijd, meestal, soms, zelden of nooit geldt.

(omcirkel één cijfer op elke regel)

		Altijd	Meestal	Soms	Zelden	Nooit
17.	**Krijgt u minder voor elkaar**, vanwege uw gezichtsvermogen, dan u zou willen?	1	2	3	4	5
18.	Bent u, vanwege uw gezichtsvermogen, **beperkt** in hoe lang u kunt werken of andere activiteitenunt volhouden?	1	2	3	4	5
19.	In hoeverre weerhoudt pijn of ongemak **in of rond de ogen**, bijvoorbeeld branden, jeuken of pijn, u ervan om de dingen te doen die u zou willen doen?	1	2	3	4	5

Omcirkel na elk van de volgende uitspraken het voor u meest passende antwoord om aan te geven dat de uitspraak voor u helemaal juist is, over het algemeen juist is, over het algemeen onjuist is, of helemaal onjuist is, of dat u het niet zeker weet.
(omcirkel één cijfer op elke regel)

		Hele-maal juist	Over het algemeen juist	Weet het niet zeker	Over het algemeen onjuist	Hele-maal onjuist
20.	Ik blijf vanwege mijn gezichts-vermogen **meestal thuis**	1	2	3	4	5
21.	Ik voel me vaak **gefrustreerd** vanwege mijn gezichtsvermogen	1	2	3	4	5
22	Ik heb **veel minder controle** over wat ik doe, vanwege mijn gezichts- vermogen	1	2	3	4	5
23.	Vanwege mijn gezichtsvermogen moet ik **teveel vertrouwen over wat andere mensen me vertellen**	1	2	3	4	5
24.	Ik heb **veel hulp van anderen nodig** vanwege mijn gezichtsvermogen	1	2	3	4	5
25.	Ik maak me zorgen dat ik dingen doe, vanwege mijn gezichtsvermogen, **die mezelf of anderen in verlegenheid brengen**	1	2	3	4	5

BECK DEPRESSION INVENTORY (BDI)

Toelichting

Deze vragenlijst meet de ernst van de symptomen van de depressie. De lijst bestaat uit een aantal uitspraken die in groepen bij elkaar staan (1 t/m 21).
Leest u iedere groep aandachtig door. Kies dan bij elke groep die uitspraak die het best weergeeft hoe u zich de **afgelopen week, met vandaag** erbij gevoeld hebt. Beantwoord de vragen door het juiste cijfer te omcirkelen. Als in een groep meerdere uitspraken even goed op u van toepassing lijken, kies dan het hoogste cijfer van elk van deze uitspraken. De scores vormen tezamen uw eindscore.

Let er op dat u alle uitspraken van een bepaalde groep leest, voordat u uw keuze maakt.

1 0. Ik voel me niet verdrietig.
1 Ik voel me verdrietig.
2 Ik ben voortdurend verdrietig en ik kan het niet van me afzetten.
3 Ik ben zo verdrietig of ongelukkig dat ik het niet meer verdragen kan.

2 0. Ik ben niet bijzonder moedeloos over de toekomst.
1 Ik ben moedeloos over de toekomst.
2 Ik heb het gevoel dat ik niets heb om naar uit te zien.
3 Ik heb het gevoel dat de toekomst hopeloos is en dat er geen kans op verbetering is.

3 0. Ik voel me geen mislukking.
1 Ik heb het gevoel dat ik vaker iets verkeerd heb gedaan dan een gemiddeld iemand.
2 Als ik op mijn leven terugkijk, zie ik alleen maar een hoop mislukkingen.
3 Ik heb het gevoel dat ik als mens een volledige mislukking ben.

4 0. Ik beleef overal net zoveel plezier aan als vroeger.
1 Ik geniet niet meer zoals vroeger.
2 Ik vind nergens nog echte bevrediging in.
3 Ik heb nergens meer voldoening van.

5 0. Ik voel me niet bijzonder schuldig.
1 Ik voel me vaak schuldig.
2 Ik voel me meestal schuldig.
3 Ik voel me voortdurend schuldig.

6 0. Ik heb niet het gevoel dat ik ergens voor gestraft word.
1 Ik heb het gevoel dat ik nog wel eens gestraft zal worden.
2 Ik verwacht dat ik gestraft zal worden.
3 Ik heb het gevoel dat ik nu gestraft word.

7 0. Ik voel me niet teleurgesteld in mezelf.
1 Ik ben teleurgesteld in mezelf.
2 Ik walg van mezelf.
3 Ik haat mezelf.

8 0. Ik heb niet het gevoel dat ik slechter ben dan iemand anders.
1 Ik heb kritiek op mezelf vanwege mijn zwakheden of fouten.
2 Ik geef mezelf steeds de schuld van mijn gebreken.
3 Ik geef mezelf de schuld van al het slechte dat er gebeurt.

9 0. Ik overweeg absoluut niet om een eind aan mijn leven te maken.
1 Ik overweeg wel eens om een eind aan mijn leven te maken, maar ik zou dat nooit doen.
2 Ik zou een eind aan mijn leven willen maken.
3 Ik zou een eind aan mijn leven maken als ik de kans krijg.

10 0. Ik huil niet meer dan normaal.
1 Ik huil nu meer dan vroeger.
2 Ik huil nu voortdurend.
3 Ik kon vroeger wel huilen, maar nu kan ik het niet meer, ook al wil ik het wel.

11 0. Ik erger me niet meer dan anders.
1 Ik raak sneller geërgerd of geprikkeld dan vroeger.
2 Ik erger me tegenwoordig voortdurend.
3 Ik erger me helemaal niet meer aan dingen waaraan ik mij vroeger ergerde.

12 0. Ik heb mijn belangstelling voor andere mensen niet verloren.
1 Ik heb nu minder belangstelling voor andere mensen dan vroeger.
2 Ik heb mijn belangstelling voor andere mensen grotendeels verloren.
3 Ik heb mijn belangstelling voor andere mensen helemaal verloren.

13 0. Ik neem nu nog net zo gemakkelijk beslissingen als vroeger.
1 Ik stel het nemen van beslissingen meer uit dan vroeger.
2 Ik heb meer moeite met het nemen van beslissingen.
3 Ik kan helemaal geen beslissingen meer nemen.

14 0. Ik heb niet het gevoel dat ik er minder goed uitzie dan vroeger.
1 Ik maak me er zorgen over dat ik er oud en onaantrekkelijk uitzie.
2 Ik heb het gevoel dat mijn uiterlijk blijvend veranderd is, waardoor ik er onaantrekkelijk uitzie.
3 Ik geloof dat ik er lelijk uitzie.

15 0. Ik kan mijn werk ongeveer even goed doen als vroeger.
1 Het kost me extra inspanning om ergens aan te beginnen.
2 Ik moet mezelf er echt toe dwingen om iets te doen.
3 Ik ben helemaal tot niets meer in staat.

16 0. Ik slaap even goed als vroeger.
1 Ik slaap niet zo goed als vroeger.
2 Ik word 's morgens één tot twee uur eerder wakker dan gewoonlijk en kan moeilijk weer in slaap komen.
3 Ik word uren eerder wakker dan vroeger en kan dan niet meer in slaap komen.

17 0. Ik word niet sneller moe dan anders.
1 Ik word eerder moe dan anders.
2 Ik word moe van bijna alles wat ik doe.
3 Ik ben te moe om ook maar iets te doen.

18 0. Ik hen niet minder eetlust dan anders.
1 Ik heb minder eetlust dan vroeger.
2 Ik heb veel minder eetlust dan vroeger.
3 Ik heb helemaal geen eetlust meer.

19 0. Ik ben zo goed als niet afgevallen de laatste tijd of ik probeer af te vallen door minder te eten.
1 Ik ben meer dan 2 kilo afgevallen.
2 Ik ben meer dan 4 kilo afgevallen.
3 Ik ben meer dan 6 kilo afgevallen.

20 0. Ik maak me niet meer zorgen over mijn gezondheid dan anders.
1 Ik maak me zorgen over lichamelijke problemen, bijvoorbeeld als ik ergens pijn voel, als mijn maag van streek is, als ik last heb van verstopping enz.
2 Ik maak me veel zorgen over mijn lichamelijke problemen en het valt niet mee om aan iets anders te denken.
3 Ik maak me zoveel zorgen over mijn lichamelijke problemen dat ik aan niets anders meer kan denken.

21 0. Ik ben me niet bewust dat er de laatste tijd iets is veranderd aan mijn belangstelling voor seks.
1 Ik heb minder belangstelling voor seks dan vroeger.
2 Ik heb tegenwoordig veel minder belangstelling voor seks.
3 Ik heb mijn belangstelling voor seks helemaal verloren.

SSL-I (SOCIALE STEUN LIJST – INTERACTIES)

Nu volgt een lijst vragen waarin telkens over 'men' gesproken wordt. Het is de bedoeling dat u onder 'men' telkens de mensen waar u mee omgaat (dus het geheel van familieleden, vrienden, kennissen, buren, collega's enz.) verstaat. Wilt u het cijfer omcirkelen dat het beste bij u past.

1 Zelden of nooit
2 Af en toe
3 Regelmatig
4 Erg vaak

Gebeurt het wel eens dat men:

1.	U aanhaalt	1	2	3	4
2.	U om raad vraagt	1	2	3	4
3.	U een ruggesteuntje geeft	1	2	3	4
4.	U laat merken wat er van u verwacht wordt	1	2	3	4
5.	U ergens heen brengt	1	2	3	4
6.	U opmontert / opvrolijkt	1	2	3	4
7.	U knuffels / liefkozingen geeft	1	2	3	4
8.	U een luisterend oor biedt	1	2	3	4
9.	U vraagt ergens aan mee te doen	1	2	3	4
10.	U een duwtje in de goede richting geeft	1	2	3	4
11.	U goede raad geeft	1	2	3	4
12.	Aan u spulletjes of een klein bedrag leent	1	2	3	4
13.	U zomaar opbelt of een praatje met u maakt	1	2	3	4
14.	U complimenten geeft	1	2	3	4
15.	U in vertrouwen neemt	1	2	3	4
16.	U om hulp vraagt	1	2	3	4
17.	U zegt dat u moet volhouden	1	2	3	4
18.	U informatie geeft over waar u iets kunt krijgen	1	2	3	4
19.	Gezellig bij u op bezoek komt	1	2	3	4
20.	U hulp biedt in bijzondere gevallen, zoals bij ziekte, verhuizing, kinderen uitbesteden enz.	1	2	3	4
21.	Aan u grote dingen zoals een auto of een groot bedrag leent	1	2	3	4
22.	U advies geeft bij allerlei huishoudelijkeprobleempjes	1	2	3	4
23.	Samen met u gaat winkelen, naar een film of wedstrijd gaat, of zomaar een dagje uit gaat	1	2	3	4
24.	Genegenheid voor u toont	1	2	3	4
25.	U opbouwende kritiek geeft	1	2	3	4

26. U troost	1	2	3	4
27. U laat begrijpen waarom u iets niet goed deed	1	2	3	4
28. Uw advies opvolgt	1	2	3	4
29. U helpt uw problemen te verhelderen	1	2	3	4
30. Uw sterke punten naar voren haalt	1	2	3	4
31. U informatie over uw gedrag geeft	1	2	3	4
32. U praktische hulp biedt bij alledaagse dingen, zoals in het huishouden of bij een klusje	1	2	3	4
33. U uitnodigt voor een feestje of etentje	1	2	3	4
34. U gerust stelt	1	2	3	4
35. Koel reageert	1	2	3	4
36. Een afspraak met u niet nakomt	1	2	3	4
37. Afkeurende opmerkingen tegen u maakt	1	2	3	4
38. U dingen verwijt	1	2	3	4
39. U onrechtvaardig behandelt	1	2	3	4
40. Onredelijke eisen aan u stelt	1	2	3	4
41. Zich teveel met u bemoeit	1	2	3	4

SSL-D (SOCIALE STEUN LIJST – DISCREPANTIES)

Bij de volgende vragen gaat het erom in welke mate het gedrag, de reactie van mensen waar u mee omgaat, afwijkt van wat u zou wensen. Het is de bedoeling dat u bij de vragen denkt aan alle mensen waar u mee omgaat (dus het geheel van familieleden, vrienden, kennissen, buren, collega's enz.). Wilt u het cijfer omcirkelen dat het beste bij u past.

1 Mis ik, zou ik graag meer willen
2 Mis ik niet echt, maar het zou prettig zijn als het
3 iets vaker gebeurde
4 Precies goed zo; ik zou niet vaker of minder vaak willen
5 Gebeurt te vaak; het zou prettig zijn als het minder vaak gebeurde

1.	U aanhalen	1	2	3	4	5
2.	U om raad vragen	1	2	3	4	5
3.	U een ruggesteuntje geven	1	2	3	4	5
4.	U laten merken wat er van u verwacht wordt	1	2	3	4	5
5.	U ergens heen brengen	1	2	3	4	5
6.	U opmonteren / opvrolijken	1	2	3	4	5
7.	U knuffels / liefkozingen geven	1	2	3	4	5
8.	U een luisterend oor bieden	1	2	3	4	5
9.	U vragen ergens aan mee te doen	1	2	3	4	5
10.	U een duwtje in de goede richting geven	1	2	3	4	5
11.	U goede raad geven	1	2	3	4	5
12.	Aan u spulletjes of een klein bedrag lenen	1	2	3	4	5
13.	U zomaar opbellen of een praatje met u maken	1	2	3	4	5
14.	U complimenten geven	1	2	3	4	5
15.	U in vertrouwen nemen	1	2	3	4	5
16.	U om hulp vragen	1	2	3	4	5
17.	U zeggen dat u moet volhouden	1	2	3	4	5
18.	U informatie geven over waar u iets kunt krijgen	1	2	3	4	5
19.	Gezellig bij u op bezoek komen	1	2	3	4	5
20.	U hulp bieden in bijzondere gevallen, zoals bij ziekte verhuizing, kinderen uitbesteden enz.	1	2	3	4	5
21.	Aan u grote dingen zoals een auto of een groot bedrag lenen	1	2	3	4	5
22.	U advies geven bij allerlei huishoudelijke probleempjes	1	2	3	4	5
23.	Samen met u gaan winkelen, naar een film of wedstrijd gaan, of zomaar een dagje uit gaan	1	2	3	4	5
24.	Genegenheid voor u tonen	1	2	3	4	5
25.	U opbouwende kritiek geven	1	2	3	4	5

26. U troosten	1	2	3	4	5
27. U laten begrijpen waarom u iets niet goed deed	1	2	3	4	5
28. Uw advies opvolgen	1	2	3	4	5
29. U helpen uw problemen te verhelderen	1	2	3	4	5
30. Uw sterke punten naar voren halen	1	2	3	4	5
31. U informatie over uw gedrag geven	1	2	3	4	5
32. U praktische hulp bieden bij alledaagse dingen, zoals in het huishouden of bij een klusje	1	2	3	4	5
33. U uitnodigen voor een feestje of etentje	1	2	3	4	5
34. U geruststellen	1	2	3	4	5