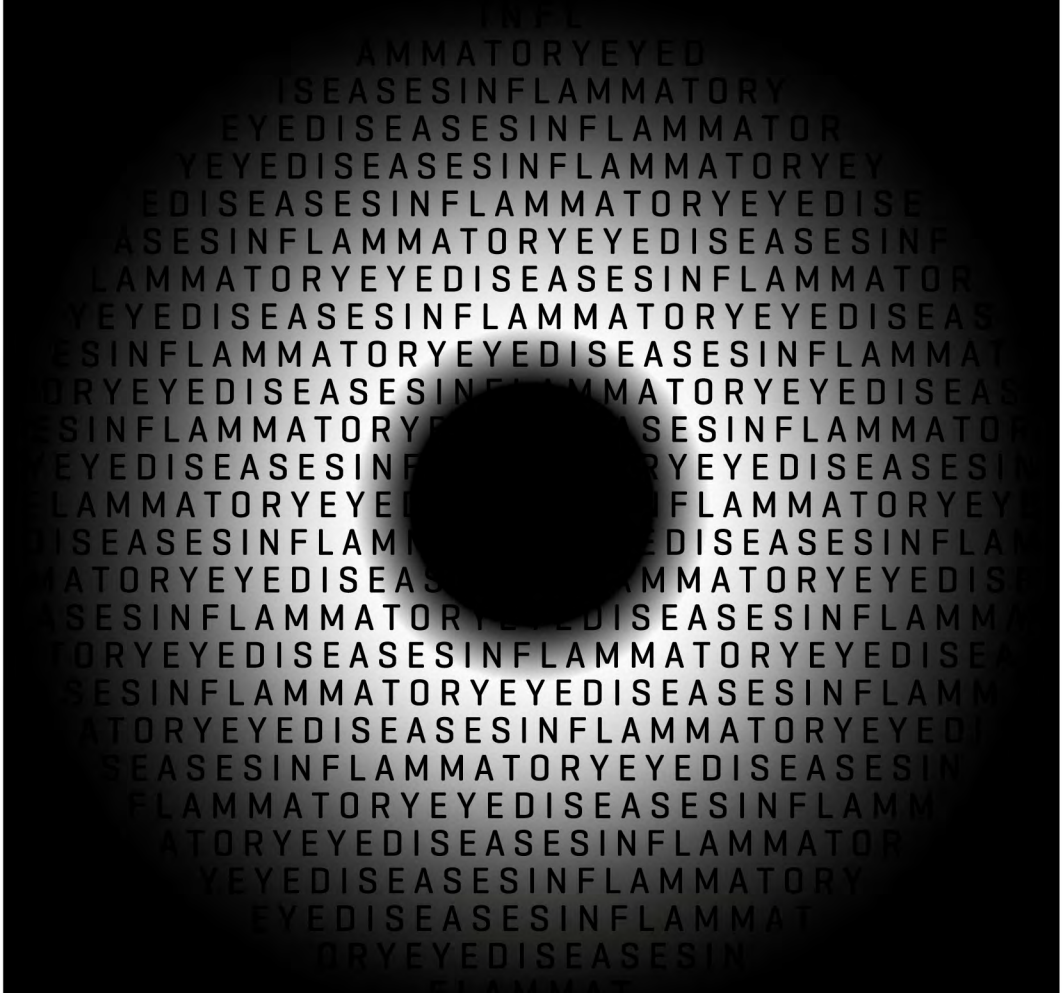
DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN INFLAMMATORY EYE DISEASES



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Diagnostic and therapeutic challenges in inflammatory eye diseases

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Colophon

Graphic design: www.studioanne-marijn.com
Printed by: Gildeprint, Enschede

ISBN printed version: 9789463236218
ISBN digital version: 9789463236225

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

rijksuniversiteit
groningen

Diagnostic and therapeutic challenges in inflammatory eye diseases

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 13 mei 2019 om 14.30 uur

door

Wietse Grieco Wieringa

geboren op 26 april 1972
te Leens

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GENERAL INTRODUCTION

1 GENERAL INTRODUCTION

GENERAL INTRODUCTION

Scleritis and uveitis are inflammatory eye-diseases which can threaten vision. In general, inflammatory eye-diseases can be triggered by auto-immune disease, infections, masquerade syndromes presenting as inflammatory eye-disease, medication, trauma and repeated ocular surgery [1 - 3]. Scleritis and uveitis can occur at any age so the burden of visual loss, the uncertain prognosis of the eye-disease and its complications and the side-effects of treatment on daily life are profound [4 - 7].

Epidemiology of scleritis

Published epidemiologic data about the incidence and prevalence of scleritis in adults is scarce [8]. The estimated reported annual incidence of scleritis is between 4 to 6 per 100,000 person-years [8, 9]. This scarcity of epidemiologic data confirms that scleritis is a rare condition. Studies on scleritis are hampered by disease severity, its rarity and the intense pain reported by most patients suffering from scleritis [2, 8]. Scleritis as an expression of underlying auto-immune disease such as rheumatoid artritis or granulomatosis with polyangiitis is the most common [2, 8]. Loss of vision is more common in eyes with posterior or necrotizing scleritis and a loss of 2 or more lines Snellen visual acuity despite optimal treatment has been noted in 30% of patients [2]. Patients with severe disease often have multiple causes for loss of visual function, such as corneal involvement, cataract, glaucoma, maculopathy, papilledema or retinal detachment [2, 8, 10]. Information about the incidence of scleritis in children is even less available. One study reported that 1.2% of all scleritis cases are found in children [11] and others reported a female preponderance [12, 13]. Among subtypes, posterior scleritis is relatively common in children [11]. Although there is no literature supporting this, outcome and disease development in pediatric scleritis are probably worse than outcome and disease development in adults. It seems likely that children with scleritis have a greater risk of visual loss due to the higher reported incidence of posterior scleritis and a greater risk of ocular complications related to longer life expectancy and disease duration in this chronic disease. Pharmacological developments in the treatment of auto-immune diseases such as rheumatoid arthritis are promising. Hopefully, patients with scleritis can benefit from this.

Epidemiology of uveitis

The overall reported annual incidence of uveitis is between 17 and 52 per 100,000 person-years and the prevalence is 38 to 714 cases per 100,000 persons [14]. The variation in reported incidences and prevalences between publications is due to variations worldwide in several predisposing factors such as genetic, geographic, social and environmental factors [14, 15]. It has been estimated that uveitis accounts for about 10% of the visual handicap in the Western world, and up to 35% of all uveitis patients have been reported to suffer significant visual impairment or

legal blindness [16]. More recent publications on long-term clinical outcome in adults show more favorable visual outcomes due to improved treatment options [17]. Uveitis in children is relatively uncommon and accounts for 5 to 10% of the total uveitis population [14, 18]. The reported annual incidence is 4 per 100,000 population and the prevalence 28 per 100,000 population [18]. It is estimated that in the western world 17-28% of the children with uveitis become legally blind in one eye [19, 20]. Uveitis in childhood offers specific challenges when compared to uveitis in adults [21]. The risk of poorer visual outcome is possibly greater in children when compared to adults [21]. In most cases of uveitis in childhood the uveitis is related to juvenile idiopathic arthritis (JIA) [20]. The onset is insidious in most cases of JIA-uveitis and diagnosis is often delayed resulting in deterioration of the visual prognosis [22]. Ocular complications such as cataract, glaucoma, band keratopathy and amblyopia may silently develop and are reported in up to 50% of children with uveitis [20, 21].

Diagnosis of inflammatory eye disease.

Early diagnosis of inflammatory eye disease and start of adequate therapy are the most important factors improving visual outcome. Diagnosis of scleritis is usually suspected from the clinical history with severe pain as a hallmark, and is confirmed by its characteristic clinical signs [2, 8]. Scleritis is classified by its anatomic location and clinical appearance (table 1) [23].In case of posterior scleritis clinical signs may be less obvious and evaluation by ultrasonography or other imaging techniques are necessary [2].The main differential diagnosis of scleritis is episcleritis. Episcleritis is usually a mild non-vision threatening form of inflammation of the superficial episcleral tissue, for which no treatment is required in most cases [2, 8]. The diagnosis in uveitis is more difficult. There are various etiologies and the systemic associations of uveitis differ between adults and children [14, 18, 24]. In general, the differential diagnosis of uveitis is based upon the anatomical location of the inflammation (Table 2) [25], the recognition of specific ophthalmic clinical signs and the outcome of the different serological tests and – when necessary – outcome of analysis of intra-ocular fluid.

Table 1. Classification of scleritis [23]

Anterior scleritis
Diffuse
Nodular
Necrotizing
Scleromalacia
Posterior scleritis (incl SINS[a])
Posterior
Surgery induced (SINS)
Panscleritis (anterior + posterior)

[a]SINS = surgically-induced necrotizing scleritis

Table 2. Classification of uveitis [25]

Anatomic location uveitis
Anterior uveitis
Intermediate uveitis
Posterior uveitis
Pan uveitis

Treatment in general

The treatment of inflammatory eye diseases depends on the etiology and possible underlying disease. In many cases, the uveitis or scleritis are part of an autoimmune process. The treatment is aimed at suppressing the inflammatory response and limiting the resulting damage. For scleritis, local therapy is insufficient and systemic therapy is required, although in some cases of non-infectious anterior scleritis a subconjunctival injection with corticosteroids can be given [26]. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed as the first step in the treatment of scleritis. In case of unsatisfactory therapeutic response, the next step is administration of oral corticosteroids at high doses for a short period of time. If prolonged treatment is necessary or in case of contraindications for corticosteroids, steroidsparing immunosuppressive drugs such as methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine, cyclosporine, and sometimes cyclophosphamide are used, often in combination with low-dose corticosteroids. In refractory or therapy resistant ocular inflammatory eye disease, tumor necrosis factor (TNF- α) antagonists such as infliximab and adalimumab or chimeric monoclonal antibodys targeted on B lymphocytes like rituximab, are increasingly being used, [27 - 31] sometimes in combination with other steroid- sparing immunosuppressive drugs.

For the treatment of uveitis, the first step in treatment are topical corticosteroids. If these are insufficient, local corticosteroid injections can be considered. Systemic corticosteroids are started in the case of severe uveitis or in case of failure of topical therapy. In case of chronic uveitis or underlying systemic disease, steroid-sparing immunosuppressive medication is required to maintain disease remission and to avoid the side effects of prolonged oral corticosteroids. Methotrexate (MTX) is the steroid sparing immunosuppressive agent of first choice in almost all cases of non-infectious uveitis [32 - 34]. If MTX is ineffective or side effects occur, a switch towards another steroid sparing immunosuppressive agent such as mycophenolate mofetil (MMF), azathioprine or cyclosporine can be made. In persistent active uveitis despite treatment, tumor necrosis factor (TNF-α) antagonists such as infliximab and adalimumab and others are increasingly being used [20, 35]. When the scleritis or uveitis has developed as a result of an infectious process, the primary treatment is aimed at the infectious pathogens. When the treatment against the infectious process starts, systemic immune suppression may additionally be necessary to reduce the inflammatory response - and thus reduce the resulting damage .

Outcome

Inflammatory eye diseases are still a leading cause of visual impairment [36, 37]. The main goal of the treatment of inflammatory eye diseases is to maintain visual function by reducing the inflammation and by the timely treatment of complications such as glaucoma, macular edema, and cataract [14 ,35]. Visual

outcome is measured as visual acuity. In case of posterior and panuveitis or secondary glaucoma, visual outcome can be impaired by visual field loss through loss of function in the affected tissues by the inflammation itself or by damage to the optic nerve as a result of high intra-ocular pressure. Loss of vision and side effects of systemic treatment are related to loss of health-related quality of life (HR QoL) in children and adults with uveitis [4, 38 - 41]. It has been suggested that the effects of uveitis on HR QoL in children are similar to those of children with other chronic conditions [42] and the disease burden of uveitis can affect quality of life even when there is no loss of vision [42].

Aims and outline of this thesis

The aim of this thesis is to improve the care for patients with inflammatory eye disease on a number of aspects. This thesis consists of 2 parts and describes studies on both the diagnostic and therapeutic challenges in the treatment and counseling of patients with inflammatory eye disease. In the first part the focus is on scleritis and uveitis in the adult population, the second part concerns uveitis in childhood. The first 3 chapters are about improving the diagnostic and therapeutic process in adult patients with rare inflammatory eye diseases such as scleritis, syphilitic uveitis and retinal dystrophies masquerading as intermediate uveitis. In the 3 chapters of the second part, efficacy and outcomes of different dosages of methotrexate (MTX) in non-infectious pediatric uveitis are evaluated, physical and psychosocial outcomes in pediatric uveitis are analyzed and risk factors for the development of secondary glaucoma in childhood uveitis are addressed.

Scleritis

As mentioned before, scleritis is a rare disease. Because of this and the prompt need for treatment, there is a paucity in the literature regarding studies predicting disease-course and visual outcome, and offering guidelines for treatment. Therefore, **chapter 2** describes patient characteristics, visual outcome, ocular complications and treatment results in a cohort of 104 patients with scleritis from 2 tertiary uveitis centers in the Netherlands. Also, predictors for a worse visual outcome, the need for steroid-sparing immunosuppressive treatment and a longer period of active disease were analyzed.

Ocular syphilis

Ocular syphilis can mimic a wide range of ocular disorders [43, 44] and is a rare sexually transmitted infection (STI) nowadays accounting for 1% to 2% of all uveitis patients [45 -47]. In the pre-antibiotic era, syphilis was more common [46]. Due to the improved screening and treatment programs it almost disappeared in the western world. Data on the epidemiology of STI needs to be interpreted carefully because they are influenced by multiple factors [47]. The incidence and prevalence of the infection are affected by biological factors, such as transmission probability, infection duration and loss of protective immunity such as in HIV-positive

patients. Also, changes in sexual attitudes and behaviors and developments in service provision, treatment, interventions, diagnostic technologies and surveillance affect incidence and prevalence [47]. Ocular syphilis is a treatable disease and because of the changes in epidemiology and unpredictability of the anatomical presentation of the uveitis [43, 44, 46, 47] ocular syphilis should always be considered in the differential diagnosis of uveitis. In the current guidelines, the recommended treatment for syphilitic uveitis is intravenous benzylpenicillin which is identical to the treatment for neurosyphilis [48, 49]. Next to adequate treatment for the syphilis infection, the use of oral corticosteroids as systemic immune suppression are recommended to prevent a Jarisch-Herxheimer reaction [48, 49]. Which is a reaction on the endotoxin-like products released by the death of harmful microorganisms within the body during antibiotic treatment and most commonly characterized by acute febrile illness with headache, myalgia, chills and rigors, resolving within 24 h [48]. It is unclear if systemic immunosuppression – next to anti-syphilitic treatment - improves visual outcome in syphilitic uveitis. Favorable visual outcome is related to early diagnosis and treatment [50, 51]. The clinical presentation of ocular syphilis has been described in many publications with relatively small numbers of patients. Due to the variability in clinical presentation, the sometimes confusing interpretation of serological tests and the debatable optimal treatment of a syphilis infection, the results from a large cohort of patients with serologically proven ocular syphilis are presented in **chapter 3.** More specifically, we report on the clinical manifestations and outcome of syphilitic uveitis in 85 patients with serologically proven syphilitic uveitis from 5 different tertiary uveitis centers in The Netherlands. The factors that correlate with a worse visual prognosis or a chronic disease course and the visual outcome of the different types of treatment are reported.

Masquerade uveitis

Retinital dystrophies (RD) are a rare group of progressive hereditary retinal degenerative diseases characterized by progressive degeneration of retinal photoreceptors leading to profound visual loss and blindness in middle or later life [52]. Worldwide, the prevalence of RD is approximately 1 in 3,000 individuals [53, 54]. The diagnosis is made by recognition of the typical clinical picture, complaints of nyctalopia, a family history of retinal degenerative disease, visual field testing and a full-field electroretinogram (ERG). In most cases of advanced RD a progressively deteriorating ERG pattern is found, characterized by undetectable rod response and reduced cone response. In uveitis, the ERG response depends on the anatomical location of the uveitis. Most frequently, reduced amplitudes of a and b waves with long implicit times are found. In some cases, the ERG response normalizes with treatment, whereas in others it stays permanently abnormal [55]. A retinal dystrophy can present itself with intraocular inflammation and cystoid macular edema masquerading as intermediate uveitis [56]. Ongoing research suggests that in CRB1-linked retinal dystrophy masquerading as

intraocular inflammation, the disease is accompanied by molecular activation of inflammatory cytokine pathways and immune cells in the blood [56 - 58]. These results on the role of inflammation in RD will hopefully provide insight in and possibilities for the treatment of RD and its complications in the future. At present, there are no treatment options besides corticosteroids and acetazolamide for macula edema and counseling of the patient. Nevertheless, patients can benefit from an early diagnosis which may result in more adequate counseling of the patient, and avoidance of prolonged treatment with high doses of immunosuppressive medication for a supposed uveitis. In **chapter 4** the diagnostic process, clinical characteristics and outcome of 6 patients from 3 different tertiary uveitis centers in The Netherlands with retinal dystrophy presenting as intermediate uveitis are reported. This study intends to improve the diagnostic process and to provide insight into the specific characteristics and clinical signs in this patient group.

Methotrexate in pediatric non-infectious uveitis

Methotrexate (MTX), due to its effectiveness, long track record [59] and good safety profile, is the steroid-sparing agent of first choice in almost all cases of non-infectious inflammatory eye diseases [32-34]. MTX is effective in about 70% of patients [32-34] and it is usually given orally or subcutaneously. The bioavailability of oral MTX varies per patient and appears to decrease at higher doses due to limits in absorption in the gastrointestinal tract [60 - 62]. Several studies in rheumatoid arthritis (RA) indicate that MTX exerts its effect by influencing multiple inflammatory pathways [63 - 65]. Firstly, MTX undergoes polyglutamation within the cells, after that MTX and its polyglutamates inhibit purine and pyrimidine synthesis, reduce antigen-dependent T-cell proliferation, and promote release of adenosine which in turn activates receptors on macrophages and neutrophils to decrease the release of proinflammatory cytokines and elevate the secretion of anti-inflammatory molecules. It is unclear if these mechanisms of action of MTX in RA are similar to uveitis [66]. But, due to its known [32-34] efficacy in ocular inflammation it is likely that the extraocular effects of MTX on the immune system provide the primary therapeutic mechanism by which systemically administered MTX affects ocular inflammation [34]. Systemic administration of MTX leads to detectable intraocular MTX levels [67, 68] and the efficacy of intra-ocular MTX on uveitis and cystoid macular edema has been described in the literature [69, 70]. However, the current evidence about dosage, duration of treatment and best route of administration for MTX in ocular inflammation is limited [32 - 34]. Also, there are concerns in the treatment of RA that since the introduction and advent of TNF inhibitors MTX is less aggressively dosed, duration of use is shorter and a more rapid escalation to biologicals is made [62, 71, 72]. In **chapter 5** we present the results of our study on the efficacy of high dose in comparison to low dose MTX in 42 pediatric patients with non-infectious uveitis. Outcome measures are time to disease remission, steroid-sparing effect and side effects.

Physical and psychosocial health in pediatric uveitis patients

Patients with auto-immune diseases are more physically inactive compared to the general population [73]. Also, aerobic fitness in children with different types of chronic conditions is reduced and they report more fatigue and lower health related quality of life (HR QoL) [74--77]. In the developed countries the majority (41.5%) of the pediatric uveitis cases are related to juvenile idiopathic arthritis (JIA) [18, 78]. Systemic immunosuppressive treatment in children with idiopathic uveitis who do not respond sufficiently to topical therapy is comparable to that used in the treatment of JIA. In JIA, children are found to be less physically active and have reduced physical fitness levels [79] which does not restore after remission has been reached [80, 81]. The causes of these persistent impairments of physical fitness and physical activity are not known, but it has been suggested that a combination of disease-related factors, treatment (e.g., medication), hypo-activity, and deconditioning could be involved [82 - 84]. Hypoactive children are often at greater risk of preventable health problems, such as obesity and cardio-metabolic diseases [82, 85].This higher risk of cardiovascular diseases is increased by the inflammation itself, circulating cytokines and the use of systemic immunosuppressive medication [83, 84, 86, 87]. Cardiovascular health in children can be improved by sufficient physical activity (PA) and physical fitness [88], whereas PA also has a beneficial effect on HR-QoL[73]. The use of systemic immunomodulatory treatment or the presence of co-morbidity other than uveitis, did negatively influence general HR QoL scores in adult uveitis patients [4, 6]. Also, in adolescents with non-infectious uveitis despite quiescence of disease and good visual function, certain factors, such as a high number of recurrences, chronicity of the uveitis and fear of blindness were correlated with a decreased HR QoL [39, 40]. Fatigue is also highly present in patients with JIA and is related to many factors including PA, physical fitness and HR QoL of which cause and effect are not exactly known [89]. In the literature, there are no publications about the physical fitness in children with uveitis and the information on the psychosocial health of children with uveitis is scarce [7, 41, 90, 91]. To add to a better understanding and treatment of the effects of a chronic disease - like uveitis - on a child's life, we present the results of our study on physical fitness, physical activity and psychosocial health in 23 children with uveitis **in chapter 6**.

Secondary glaucoma in pediatric uveitis

Childhood uveitis has an inherent predisposition to develop secondary glaucoma, with a prevalence of 5-13.5% [92]. Secondary glaucoma occurs when uveitis is associated with raised intraocular pressure (IOP) and optic nerve damage, resulting in irreversible visual field loss and possible visual impairment [93]. The damage to the trabecular system by the inflammation, but also the use of topical steroids as treatment of uveitis can increase the IOP. Secondary glaucoma in childhood uveitis has an unpredictable course, with large IOP fluctuations, varying responses to eye-pressure lowering medication and a frequent steroid-

response [94]. Increased IOP is initially treated pharmacologically by using topical anti-glaucoma medication. If pharmacological treatment of IOP is insufficient, glaucoma surgery is required. Only small studies have investigated the risk factors of developing secondary glaucoma in childhood uveitis. Two studies reported a female preponderance, JIA as the most common etiology and anterior uveitis as the predictive anatomical site in the glaucoma group [92, 95]. Another small study compared the need of glaucoma surgery in children with uveitis who developed secondary glaucoma. Both mean age and the average number of previous intraocular surgeries in the surgery group were significantly higher than in the control group [96]. To obtain the best long-term visual outcome, it is important to identify children with refractory glaucoma at an early stage and to treat them by glaucoma surgery before irreversible damage has occurred [97]. In **chapter 7** the results of our study on the possible risk factors for the development of secondary glaucoma needing glaucoma surgery are reported. The study was conducted in a large cohort of 196 children with uveitis from 2 tertiary uveitis centers in the Netherlands.

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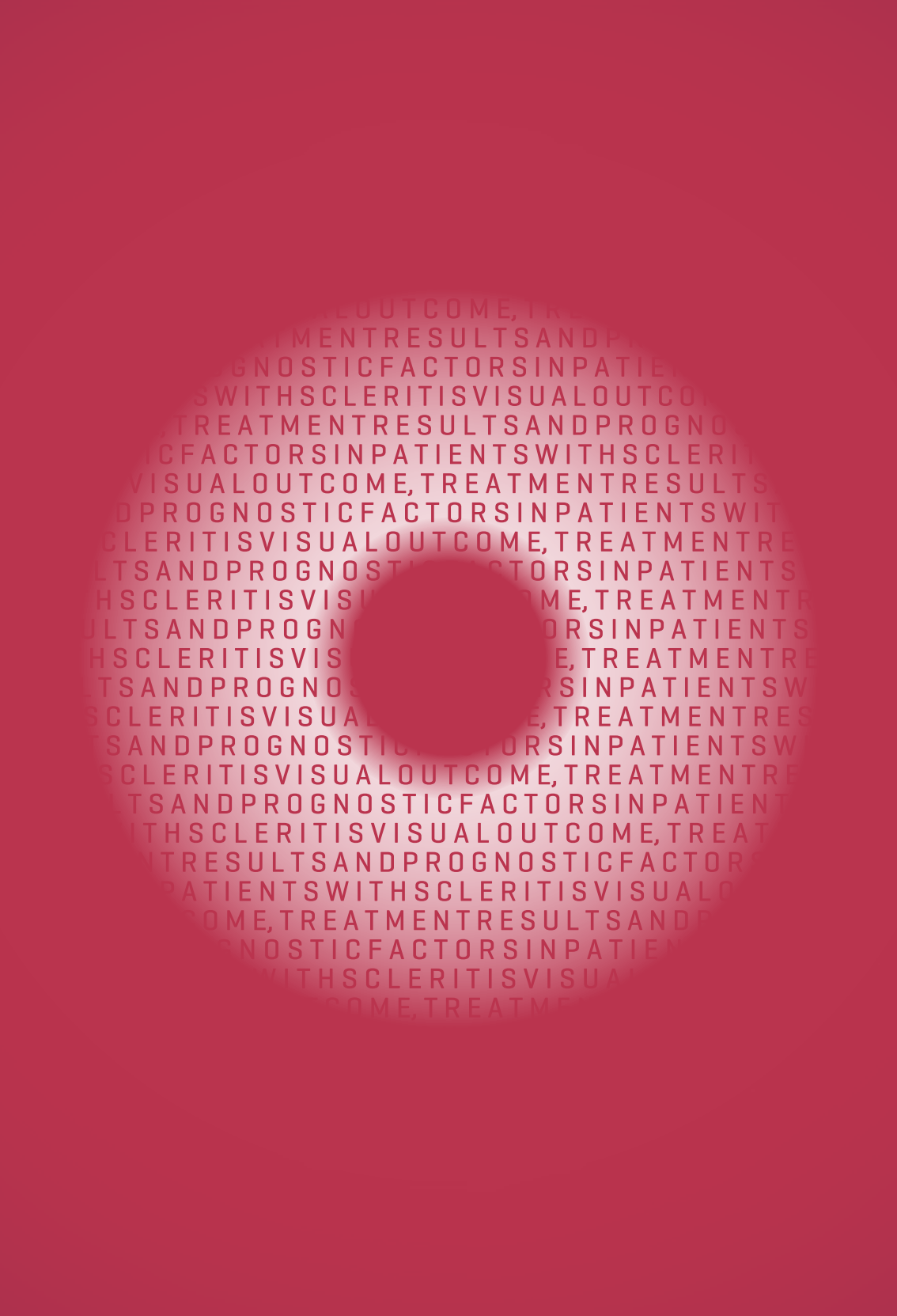

2

VISUAL OUTCOME, TREATMENT RESULTS AND PROGNOSTIC FACTORS IN PATIENTS WITH SCLERITIS

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Ophthalmology. 2013 Feb;120(2):379-86

ABSTRACT

Purpose: To analyze the visual outcome, systemic associations, effectiveness of treatment and predicting features of 104 scleritis patients.
Design: Retrospective case series.
Participants: 104 patients treated for scleritis at the University Medical Centers of Groningen and Utrecht.
Methods: The clinical records of 104 patients diagnosed with scleritis between 1992 and 2011 at the University Medical Centers of Groningen, (n= 64) and Utrecht (n=40) were retrospectively analyzed.
Main outcome measures: Loss of visual acuity, ocular complications, related systemic disease, type of treatment, time to treatment success and predictive features.
Results: Mean age was 51.5 (standard deviation[SD], ±13.6) years, 63 (60.6 %) patients were female. Mean follow up was 38.2 (SD± 33.8) months. A loss of more than two lines of Snellen acuity was observed in 23 patients, 3 of whom had a final visual acuity of no light perception (NLP). In general, patients with necrotizing scleritis (n=15) had a poorer outcome.
Ocular complications were observed in 88 (84.6%) patients. Underlying systemic disease was identified in 34 (32.7 %) patients. Steroid-sparing immunosuppressive medication was used in 47 patients, 36 of these were treated with methotrexate (MTX). This led was successful in 17 (47.2%) patients over the course of a mean ± SD 103.7 ± 83.7 weeks. Mycophenolate mofetil (MMF) was the treatment in 10 patients, and in 5 patients treatment success was achieved in a mean ± SD 65.3 ± 37.4 weeks. Treatment with tumor necrosis factor-alpha (TNF-α) antagonists led to treatment success in a mean ± SD 32.6 ± 21.8 weeks in 5 of the 11 treated patients. Patients with loss of visual acuity or those treated with oral steroid-sparing immunosuppressive drugs had more often an underlying associated disease, a bilateral scleritis and a longer period of symptoms at presentation.
Conclusions: Scleritis is a severe ocular inflammation often associated with ocular complications. In this population roughly half of the patients were treated with systemic immunosuppressive medication. MMF and TNF-α antagonists can be used in case of MTX-failure. TNF-α antagonists seemed to be more effective than MTX. Within this group, an underlying associated disease, a bilateral scleritis and a longer period of symptoms at presentation were predictive features for a more severe disease course.

INTRODUCTION

Scleritis is a rare, usually painful inflammation of the sclera that can threaten vision.[1] Scleritis is still classified according to the classification proposed by Watson and Hayreh[2] in 1976 based on anatomic location and appearance (Table 1). Few patients convert from episcleritis to scleritis,[2,3] and only a small group of scleritis patients change from one variant of scleritis to another.[3] Complications such as corneal and scleral thinning, corneal ulcers, serous retinal detachment, papilledema, glaucoma, cataract, and uveitis frequently are seen.[4,5] In 40% to 50% of patients, scleritis is an expression of an underlying systemic disease.[5] Rheumatoid arthritis, Wegener's disease, relapsing polychondritis, systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa, and seronegative spondylarthropathies[5,6] are the most common autoimmune causes. In 4% to 18% of patients, an infectious cause is found, of which herpes zoster is the most frequent cause, followed by tuberculosis, syphilis, leprosy, and Lyme borreliosis.[3,5–7] Other causes of scleritis, such as malignancies, medication, surgery, and trauma, are reported to be rare in all studies. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed as the first step in the treatment of scleritis. In case of unsatisfactory therapeutic response, the next step is administration of oral corticosteroids at high doses for a short period. If prolonged treatment is necessary or in case of contraindications for corticosteroids, steroidsparing immunosuppressive drugs such as methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine, cyclosporine, and sometimes cyclophosphamide are used, often in combination with low-dose corticosteroids. In refractory or therapy-resistant ocular inflammatory eye disease, tumor necrosis factor (TNF-α) antagonists such as infliximab and adalimumab increasingly are be-ing used,[8 –14] sometimes in combination with other steroid- sparing immunosuppressive drugs. Because of the low incidence and prevalence of scleritis,[1] the numbers of studies with large numbers of patients are limited,[15] and well-documented clinical experience in predicting the course of the disease and guidelines for its treatment are not widely available. This retrospective study examined patient characteristics, visual outcomes, ocular complications, and efficacy of treatment for 104 scleritis patients. Furthermore, prognostic factors that correlated with a worse visual prognosis, steroid-sparing immunosuppressive treatment, or prolonged disease duration were investigated.

METHODS AND PATIENTS

One hundred four patients diagnosed with scleritis between 1992 and 2011 at the University Medical Centers of Groningen, The Netherlands (n = 64), and of Utrecht, The Netherlands (n = 40), were analyzed. The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study. Patients were identified by searching on the diagnosis code 'scleritis' in the digital uveitis databases of both centers. If in doubt about the diagnosis of scleritis, the opinion of an academic uveitis specialist based on the patient's file was decisive. Only patients with a follow-up of more than 3 months were included. The Watson and Hayreh classification was used for the type of scleritis, with the diagnosis of posterior scleritis or panscleritis confirmed by ultrasound. Necrotizing scleritis was classified as necrotizing (with inflammation) or scleromalacia perforans (without inflammation).

The decimal equivalent of the Snellen visual acuity of both eyes at presentation and at last follow-up and the maximum visual acuity were recorded. This visual acuity was converted to logarithm of the minimum angle of resolution units and, after computation of mean and standard deviation, was calculated back to Snellen decimal acuity. Loss of visual acuity was defined as a decrease of more than 2 lines on the Snellen chart. No light perception in the affected eye was defined as blindness. Patients whose loss of visual acuity was not a result of the scleritis were excluded from this analysis. Corneal complications were characterized as ulcerative or peripheral thinning. Uveitis was diagnosed when cells could be observed in the anterior chamber or in the vitreous and was classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. The lens was graded as clear, having cataract, pseudophakic, or having posterior capsule opacification. The presence of cystoid macular edema was noted only if confirmed by fluorescein angiography or optical coherence tomography. Serous retinal detachments were diagnosed by funduscopy or ultrasound. Ocular hypertension was defined as an intraocular pressure of more than 21 mmHg, and the given treatment was recorded.

All 104 patients underwent screening for underlying systemic disease, and 88 patients underwent screening in accordance to the guidelines of the Dutch Ophthalmologic Society: (http://www.oogheelkunde.org/uploads/fl/ve/flvem3mKxt8ThFFYVhn8GQ/Richtlijn- voor-diagnostiek-en-behandeling-van-uveitis-15-mei-2007-1.pdf; accessed January 23, 2012). The other 16 patients were screened by a tailored approach or screening was not performed when scleritis was considered a manifestation of a known systemic disease. Laboratory testing included blood and urine tests, chest radiography, and tuberculin skin testing. Serologic and general laboratory tests included complete blood count, white cell differential, inflammatory parameters (C-reactive protein

and erythrocyte sedimentation rate), liver and kidney function tests, antinuclear antibody analysis, antineutrophil cytoplasmic antibody (ANCA) analysis, and rheumatoid factor analysis. Other tests, such as Treponema pallidum antibody titers, Lyme antibody titers, angiotensin-converting enzyme, and human leukocyte antigen (HLA)-B27, were not obtained routinely, but were based on history and physical examination. In case of an underlying systemic disease, the patient was diagnosed by a specialist in that area. Associated systemic diseases were classified as infectious or autoimmune. The most common autoimmune and infectious causes were recorded. The rare causes were listed per patient. When known, the smoking status was included in the analysis.

In these patients, treatment was administered mainly according to a stepladder approach: In infectious causes, the cause of the infection was treated. In autoimmune nonnecrotizing scleritis, NSAIDs were given as a first choice, and in case of NSAID failure, high-dose corticosteroids were given. In case corticosteroids could not be reduced to a dosage of less than 10 mg daily, a corticosteroid-sparing immunosuppressive drug was considered, which was usually MTX. Methotrexate was started orally in a dosage between 7.5 and 15 mg weekly and was increased according to clinical response to a maximum of 25 mg weekly via subcutaneous injection or 30 mg weekly orally. In most patients, this was carried out in at least 3 steps each with an interval of at least 2 months. In case of MTX failure, MMF was started, and in case this failed as well, a TNF-α antagonist was introduced. In case of necrotizing scleritis, corticosteroids and corticosteroid-sparing medication were started immediately.

Treatment success was defined as a subjective and an observable inactive disease for longer than 3 months using less than 10 mg daily oral prednisone alone or in combination with corticosteroidsparing drugs. A relapse was defined as a recurrence of the scleritis after a quiet episode described in the patient file. The total followup time (disease duration including treatment of secondary complications) and time to treatment success were documented. In case of a multiple medication regimen, a stepwise approach was used and the time to control of the inflammation was related to the last added systemic immunosuppressive drug. In patients who were already receiving systemic medication for a systemic disease at presentation, the change in medication or dosage responsible for treatment success was recorded.

How clinical characteristics, visual outcome, ocular complications, and differences in treatment affected outcome was analyzed using SPSS software version 18 (SPSS, Inc, Chicago, IL) based on 3 end points: loss of visual acuity, treatment with steroid-sparing immunosuppressive drugs, or longer disease duration. A P value of 0.05 or less was considered to be statistically significant. To assess the value and weight of the prognostic factors, the chi-square test

for categorical variables, the Student *t* test for comparing independent groups with a continuous variable, and the Spearman bivariate correlation coefficient for analysis of a correlation between 2 continuous variables were used. These findings were verified and confirmed by logistic and linear regression models. Two patients were identified by SPSS analysis (boxplot) as extreme outliers (more than 3.0 times the interquartile range above the third quartile) and therefore were excluded from the analysis. Kaplan-Meier curves were used to display graphically the type of treatment related to time to disease remission.

RESULTS

Patients' characteristics are summarized in Table 1. Of the 104 scleritis patients, 63 (60.6%) were female. Mean follow-up was 38.2 months (range, 3–154 months). Mean age was 51.5 years (range, 18–91 years). The 6 patients with necrotizing disease were the oldest; the 4 patients with posterior disease were the youngest. The latter were all female. Most patients (n = 64) had unilateral disease. Diffuse anterior scleritis was the most common type of scleritis, followed by panscleritis.

Table 2 summarizes ocular complications. Complications were observed in 88 (84.6%) patients. The largest percentage of complications were seen in necrotizing scleritis patients. Uveitis was the most common complication (n = 47). Cataract formation was documented in 30 patients, whereas 6 patients were pseudophakic at presentation. Posterior scleral swelling as shown by ultrasound was found in 31 patients, and 2 patients had posterior scleral thickening related to severe anterior scleritis.

Table 3 shows the loss of visual acuity related to type of scleritis and severity. A loss of more than 2 lines of Snellen acuity occurred in 23 patients (Table 3), 3 of whom became blind (no light perception visual acuity) because of scleritis. All 3 of the latter patients had necrotizing scleritis. In 2 of these patients, there was an association with Wegener's disease, and the third patient had a scleromalacia perforans without known underlying systemic disease.

The 23 patients with a decrease in visual acuity had an average Snellen visual acuity standard deviation (SD) at presentation of 0.9 ± 0.34, and their final average Snellen visual acuity ±SD was 0.66±0.38. The remaining 81 patients showed, on average, an increase in visual acuity of 0.17 (range, 0.007–1.0).

Of the 43 patients (Table 2) with an intraocular pressure to more than 21 mmHg, 26 patients were diagnosed as steroid responders because of the use of local or systemic corticosteroids. Because of the elevation in intraocular pressure, 20 patients were administered antiglaucoma medication, and glaucoma surgery was undertaken in 6 patients.

Table 1. Patient characteristics

Diagnosis/type	N	Mean age (range)	Male N (%)	Female N (%)	Bilateral N (%)
Scleritis total	104	51.5 (18.6 - 91.8)	41 (39.8%)	63 (60.6 %)	40 (38.5%)
Anterior scleritis	71	51.9 (25.4 – 91.8)	29 (40.8%)	42 (59.2%)	29 (40.8%)
Diffuse	36	51.4 (25.4 – 79.5)	13 (36.1%)	23 (63.9%)	18 (50%)
Nodular	20	50.1 (30.5 – 67)	7 (35%)	13 (65%)	5 (25%)
Necrotizing	6	62.5 (41.3 – 91.8)	3 (50%)	3 (50%)	3 (50%)
Scleromalacia	9	50.9 (38.6 – 71.6)	6 (66.7%)	3 (33.3%)	3 (33.3%)
Posterior scleritis (incl SINS)	7	47.9 (18.6 – 73.1)	2 (28.6%)	5 (71.4%)	1 (14.3%)
Posterior	4	39.4 (18.6 – 56.5)	0	4	1 (25%)
Surgery induced (SINS)	3	59.2 (39.8 – 73.1)	2 (66.7%)	1 (33.3%)	0
Panscleritis (anterior + posterior)	26	51.4 (25.6 – 69.2)	10 (38.5%)	16 (61.5%)	10 (38.5%)

Table 2. Ocular complications

Feature	Anterior Diffuse	Anterior nodular	Anterior necrotizing	Sclero-malacia	Posterior	Surgery Induced	Pan-scleritis	N (%)
N total	36	20	6	9	4	3	26	104
Bilateral	18	5	3	3	1	0	10	40 (38.5%)
Ocular complications	31	11	6	7	4	3	26	88 (84.6%)
Corneal Thinning	2	2	2	2	0	0	1	9 (8.7%)
Corneal ulcerative	8	2	4	2	1	0	2	19 (18.3%)
Uveitis	20	1	4	4	2	1	15	47 (45.6%)
Anterior uveitis	18	1	2	3	2	1	10	37 (35.9%)
Intermediate uveitis	2	0	0	1	0	0	1	4 (3.9%)
Panuveitis	0	0	2	0	0	0	4	6 (5.8%)
Cataract	10	2	4	5	1	0	8	30 (28.8%)
CME	5	1	3	1	1	0	11	22 (21.4%)
Exudative retinal detachment	0	0	2	1	0	0	6	9 (8.7%)
T-Sign (US)	0	1	1	0	4	0	25	31 (30.1%)
VA-loss*	10	3	2	4	0	0	4	23 (22.1%)
Ocular hypertension§	13	8	3	3	0	2	14	43 (41.7%)
Steroidresponder	9	4	2	2	0	2	7	26 (25.2%)

CME = cystoid macular edema; US = ultrasound; VA = visual acuity. *Decrease in visual acuity of 2 Snellen lines or more (worse of the 2 eyes) at the end of the follow up. § Intra-ocular pressure higher than 21 mmHg

Table 3. Vision loss related to scleritis

Diagnosis/ type	Anterior Diffuse	Anterior nodular	Anterior necrotizing	Sclero-malacia	Posterior	Surgery Induced	Pan-scleritis	N (%)
N total	36	20	6	9	4	3	26	104
Loss of ≥ 2 Snellen lines*	7	1		1			1	10 (9.6%)
Severe loss > 3 Snellen lines§	3	2		2			3	10 (9.6%)
NLP			2	1				3 (2.9%)

NLP = No light perception. * Decrease in visual acuity of ≥ 2 Snellen lines at the end of the follow up period. § Decrease in visual acuity of > 3 Snellen lines at the end of the follow up period

Underlying systemic diseases are summarized in Table 4. In 34 (32.7%) patients, an underlying cause was found. Within the noninfectious group, rheumatoid arthritis (RA) was the most frequently identified underlying disease (n = 14), followed by Wegener's disease in 7 patients. In most of the patients (n = 26) with an underlying noninfectious cause, the disease was already diagnosed before the first episode of scleritis. In 2 patients, Wegener's disease was found by screening, and in 1 patient, RA was found by screening, and in another it manifested during follow-up. In 3patients, a likely infectious cause of the scleritis was found by screening (Table 4).

Table 4. Underlying systemic disease

Systemic disease	N (%)	Present before scleritis	Diagnosis through screening	Diagnosis during follow up
Total n (%)	34 (32.7%)	26 (25%)	6 (5.8%)	2 (1.9%)
Infectious	3 (2.9%)		3 (2.9%)	
Herpes zoster	2		2	
Lues/syfilis	1		1	
Non-infectious	31 (29.8%)	26 (25%)	3 (2.9%)	2 (1.9%)
Rheumatoid arthritis	14	12	1	1
Wegener's granulomatosis	7	5	2	
Inflammatory bowel disease	3	3		
Behçet's disease	2	2		
Myastenia Gravis	1	1		
Polyarteritis Nodosa	1	1		
Relapsing Polychondritis	2	1		1
Psoriatic Arthritis	1	1		

Screening according to the guidelines of the Dutch Ophthalmologic Society (http://www.oogheelkunde.org/uploads/fl/ve/flvem3mKxt8ThFFYVhn8GQ/Richtlijn-voor-diagnostiek-en-behandeling-van-uveitis-15-mei-2007-1.pdf; accessed January 23, 2012) was performed in 88 patients. The other 16 patients were screened by a tailored approach.

Inflammatory parameters (CRP and ESR) were raised in 52 of the 93 tested patients. In 4 of the 46 tested patients, HLA-B27 positivity was found. Lues serologic level was tested in 62 patients, and in 1 patient, Treponema pallidum antibodies were found. Elevated antinuclear antibody titers were found in 22 of the 79 patients tested. Seven of these patients had an autoimmune disease. Rheumatoid factors were demonstrated in 11 of 73tested patients; 5 of these patients had RA. P or c-ANCA autoantibodies were found in 12 of the 80 patients tested. In 5 of 7 patients with Wegener's disease, an increased c-ANCA titer was found. In 64 patients, the angiotensin converting enzyme (ACE) level was determined, 1 of which was out of normal range. In 82 patients, chest radiography was performed. In 7 of them, abnormalities were found, and in 3 cases, there was a probable association between the findings and scleritis.

To describe and analyze efficacy of treatment, medication at presentation and medication used for the treatment of scleritis are summarized in Tables 5 and 6. At presentation, 31 patients were treated with combinations of different drugs. In 23 patients, NSAIDs were combined with topical steroids, and MTX was combined with NSAIDs at presentation in 6 patients. Mycophenolate mofetil was combined with MTX in 1 patient, and another patient was treated with topical steroids, topical NSAIDs, and antibiotic eyedrops at presentation. None of the patients was taking oral corticosteroids at presentation, and 49 patients were not treated at presentation (Table 5).

Table 5. medication at presentation*

Medication	N (%)
None	49 (47.5%)
Local steroids	46 (44.2%)
NSAIDs	31 (29.8%)
MTX	6 (5.8%)
AZA	4 (3.8%)
MMF	1 (1%)
Cyclosporine	1 (%)
TNF-α antagonist	3 (2.9%)
Antiviral	2 (2.9%)
Antibiotics	5 (4.8%)

AZA = azathioprine; MMF = mycophenolate mofetil: MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF-α = tumor necrosis factor α. * 31 patients were treated with combinations (see text)

Most of the patients (n = 42) who were treated with NSAIDs had no underlying disease (n = 32). Of the 42 patients treated with NSAIDs, 33 patients also were treated with topical steroids (Table 5). Subconjunctival triamcinolone acetonide injections were used in 3 patients with diffuse anterior scleritis; of these, 1 patient achieved disease remission after 3 subconjunctival injections in 47.1 weeks. Oral corticosteroids were used in 64 patients (Table 6), usually in combination with local steroids (n = 52) and sometimes incombination with NSAIDs (n = 8). For patients who used oral corticosteroids for maintenance, the dosage varied between 5 and 20 mg. On average, patients used more than 7.5 mg daily oral corticosteroids for a mean ±SD of 65 ±72.4 weeks (median, 42 weeks).

Methotrexate was used as treatment in 36 patients (Table 6). The mean dose of MTX was 19 mg weekly (median, 20 mg; range, 10–30 mg), with 1 patient using 30 mg weekly. All patients received folic acid supplementation 24 to 48 hours after their weekly dose of MTX. Treatment success was achieved in 17 of 36 patients with a mean dose of 18 mg weekly (median, 17.5 mg weekly). Within this group, there was no relationship between MTX dosage and chance of treatment success. However, the patients who received a higher dose of MTX (mean, 26.3 mg weekly) showed a smaller range in time to treatment success (range, 80–215 weeks) than the patients who were treated with a lower dose (mean, 15.6 mg weekly) of MTX (range, 21–336 weeks).

Mycophenolate mofetil was used in 10 patients as a steroidsparing immunosuppressive treatment (Table 6); 5 of these patients were treated with MMF after MTX failure. Treatment success was achieved in 5 patients in a mean ±SD of 65.3 ±37.4 weeks (median, 73 weeks). Azathioprine was added to the immunosuppressive regimen in 13 patients; treatment success was achieved in only 1 patient in 192.8 weeks. In 3 patients, a combination of immunosuppressive drugs including azathioprine resulted in treatment success. In these cases, treatment success was attributed to the last added immunosuppressive drug.

In 5 of the 11 patients who received a TNF-α antagonist, treatment success was achieved in 32.6 weeks (SD, 21.8 weeks;median, 28.9 weeks; Table 6). The remaining 6 patients had no treatment success, which was ascribed to a short follow-up time or a change in treatment. Most patients were treated with 1 or 2 other immunosuppressives in addition to a TNF-α antagonist. Only 1patient achieved treatment success with adalimumab as monotherapy. The 4 other patients achieved treatment success with a combination of etanercept and MTX, adalimumab and MTX, or adalimumab combined with MTX and cyclosporine (n = 2). One patient was started on infliximab, but still had active disease at the end of the follow-up.

Of the 8 patients treated with cyclophosphamide (Table 6), 6 had Wegener's disease. Control of inflammation was reached in 4 of these patients with a combination of oral corticosteroids, cyclophosphamide, and azathioprine or MMF in a mean±SD of 68 ± 75.7 weeks. Of the other 4 patients, 1 patient became blind (no light perception visual acuity), 1 patient died during follow-up, 1 patient had active disease, and 1 patient had control of the inflammation with a high dose of oral corticosteroids.

There were 12 patients without described treatment success. Five of these 12 patients had no known systemic disease, and the other 7 patients had RA (n = 2), Wegener's disease (n = 3), or relapsing polychondritis (n = 2). Four patients died during followup; 2 of them had RA and 1 died of ovarian carcinoma. The time and chance of treatment success related to the type of treatment was displayed graphically using Kaplan-Meier curves (Fig 1). In 27 patients, medication was discontinued or changed because of side effects. Overall, 60 patients relapsed 1.65 times (range, 0–5; median, 1).

Table 6. Medication used for scleritis treatment

Medication	N	Remission N %	Mean time till remission (weeks)
NSAID	42	36 (85.7%)	48.8 (median 19.1, min-max 12 – 228.6)
Oral corticosteroids	64	19 (29.7%)	83.9 (median 56.7, min-max 12 – 301.1)
MTX	36	17 (47.2%)	103.7 (median 93.6, min-max 21.9 – 336.7)
AZA	13	1 (7.7%)	192.8
TNF-α antagonist	11	5 (45.5%)	32.6 (median 28.9, min-max 14 – 69.6)
MMF	10	5 (50%)	65.3 (median 73, min-max 26.3 – 115.6)
Cyclophosphamide	8	4 (50%)	68 (median 35.1, min-max 21.4 – 180.4)

AZA = azathioprine; MMF = mycophenolate mofetil: MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF- α = tumor necrosis factor α.

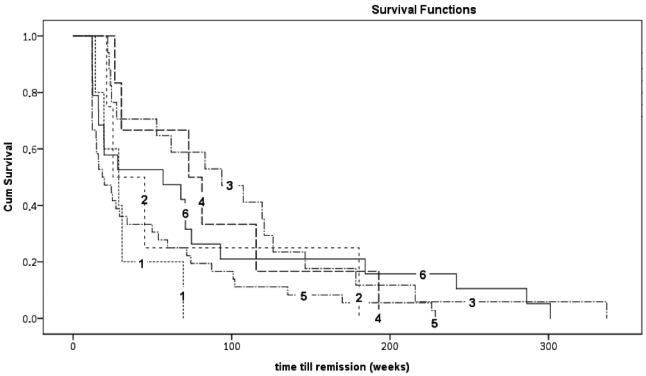

Figure 1. Kaplan-Meier curves showing the time and chance of treatment success related to the type of treatment. 1 = Tumor necrosis factor-alpha antagonists, 2 = Cyclophosphamide, 3 = Methotrexate, 4 = Mycophenolate mofetil, 5 = Nonsteroidal anti-inflammatory drugs, 6 = Oral corticosteroids.

Table 7. Prognostic factors

Characteristic	(N) %	Visual- acuity loss, P value (N)	Steroid-sparing, P value (N)	Disease duration, P value (N) [§]
Gender (female/male)	61/43	NS[‡]	NS[‡]	NS[†]
Duration of symptoms (wks), no. (range) presentation	21.7 (1-286)	NS[†]	NS[†]	P=<0.000[*]
Smoking	41 (42.6%)	NS[‡] (10)	NS[‡] (21)	NS[†]
Underlying systemic disease	34 (32.7%)	P=0.024[‡] (12)	P=<0.000[‡] (25)	NS[†]
Bilateral scleritis	40 (38.5%)	P=<0.000[‡] (17)	P=0.002[‡] (26)	P=<0.000[†]
Uveitis	47 (45.6%)	NS[‡] (12)	NS[‡] (24)	NS[†]

NS = Not significant, [‡] Chi-square test. [†] Students t-test. [*] Bivariate correlation. [§] Two extreme outliers were excluded from this analysis. One patient had a scleritis related to Wegener's disease, the other patient was suffering from a scleritis related to rheumatoid arthritis.

In the analysis of the prognostic factors (Table 7), patients with a bilateral scleritis at any time had a worse prognosis for all 3 end points. Patients with underlying systemic disease more often demonstrated loss of visual acuity and were more likely to be treated with steroid-sparing immunosuppressive drugs. In the analysis for disease duration, 2 patients had an extremely long duration of disease and were identified by SPSS software (boxplot) as extreme outliers (more than 3.0 times the interquartile range above the third quartile), and therefore they were excluded from this analysis. This analysis showed that patients who had scleritis for a longer period at presentation also had a longer disease duration after presentation.

These different prognostic factors were confirmed by logistic and linear regression models for interrelationships and influence of the different factors. In addition to this, the multivariate linear model for disease duration found

that men—although fewer—had a longer disease duration. To investigate the effect of a longer disease duration on the risk of loss of visual acuity, a separate multivariate inear model was used. In this model, a longer disease duration was not predictive of loss of visual acuity.

This analysis suggests that the strongest predictor for a worse prognosis is bilateral disease at any time. Patients with bilateral disease lost significantly more visual acuity, were treated significantly more often with steroid-sparing immunosuppressive drugs, and had a significantly longer disease duration.

DISCUSSION

Within this cohort, 23 patients (22.1 %) lost more than two lines of visual acuity on the Snellen-chart. This in contrast to the 81 patients (77.9 %) who gained visual acuity or lost less than 2 lines on the Snellen-chart. Most patients with a loss of visual acuity in our group (n=10) had a diffuse anterior scleritis. Necrotizing scleritis was the most threatening variant of scleritis. Of the 15 patients with necrotizing scleritis, 3 had a final visual acuity of no light perception and 2 lost more than 3 Snellen lines of visual acuity. In contrast to some other studies, [5, 16] panscleritis had a good prognosis and no higher association with an underlying disease. Although these findings regarding visual acuities should be interpreted cautiously in a retrospective study [17, 18], they are in concordance with the literature where loss of visual acuity is found in 15.9 to 37 % of the patients with scleritis [1, 16,19, 20].

Screening of scleritis patients for an underlying systemic disease should be aimed at the high-impact diseases such as RA and Wegener's disease. The same holds true for infectious causes: They should be identified early on because they need a different therapeutic approach. In most of the current patients, systemic disease had already been diagnosed before scleritis onset. in few of them, this was newly identified by screening, and in even fewer patients systemic disease became manifest during follow-up. Screening for HLA-B27 positivity seems questionable, because an occurrence of HLA-B27 positivity equal to that in the normal population (8%) was found and because HLA-association with scleritis is rarely described in the literature [21 - 23]. Also, the use of screening for sarcoidosis is not evident, since this is considered a rare cause of scleritis [5, 24], and in this study only one patient had elevated ACE-levels, without systemic manifestations of sarcoidosis. These findings suggest that customizing the screening for each patient seems an approach by which more useful clinical information can be obtained at lower costs.

In the scleritis patients, MTX was the most frequently used primary steroid-sparing immunosuppressive drug. The dosage of MTX did not influence the treatment success rate, but it had an effect on the range in time span to reach treatment success, with a lower range in de maximally treated group. The time to treatment success of MTX in our study was long, but it is comparable to that in other reports on scleritis [25]. However, the time to success of MTX treatment in this study was considerably longer than the reported time to treatment success of MTX in uveitis eyes [26].

Reduction in time to treatment success of MTX could be attempted by introducing a quicker dose escalation scheme including a faster switch to subcutaneous administration. The latter will result in a better bioavailability of the drug, particularly in higher MTX doses [27 - 30].

In rheumatic disorders it is recommended to start with 10-15 mg weekly, with an escalation of 5 mg every 2-4 weeks up to 20-30 mg weekly, depending on clinical response and tolerance, whereas subcutaneous administration should be considered in case of an inadequate response or intolerance [29]. Such schemes are currently being used in the treatment of RA-patients and have resulted in a reduction of the time to treatment success and a better steroid-sparing effect [27 - 29]. It has been shown that subcutaneous administration of MTX is equally as well tolerated as oral administration [28].

Reducing time to reach the maximum MTX dose will probably lead to a reduction in time to treatment success in scleritis patients. Also, MTX failure will be sooner evident, so that therapy can be switched at an earlier point in time. A reduction in time to treatment success will probably also reduce ocular complications, which mainly are the result of active disease, steroid use, or a combination of both. Whether more patients can be successfully treated with monotherapy is an issue beyond the scope of this study and one that could be studied in a comparative study.

Mycophenolate mofetil seems a viable option after MTX-failure because it can induce treatment success in an additional 50 % of the patients. It is open to discussion whether MMF in selected patients is preferable as primary therapy based on underlying systemic disease or susceptibility to side effects. However, the availability of this option also depends on local healthcare policies.

In case both options fail, TNF-α antagonists can induce control of inflammation in a further half of the patients. In case of TNF-α antagonists, time to treatment success seems to be much shorter than that needed for MTX and MMF. This suggests a more effective mechanism of action compared to MTX and MMF. Whether TNF-α antagonists can be administered as monotherapy, cannot be concluded from this study because only 1 patient received monotherapy. With

regard to TNF-α antagonists, it is not known presently which drug is preferable in the treatment of scleritis, and long-term effectiveness needs to be established as well. Most reports are on infliximab, a humanized chimeric monoclonal antibody, which was the first TNF-α antagonist introduced [8, 10, 13, 14]. Several small case-reports describe that rituximab, a genetically engineered chimeric monoclonal antibody that recognizes CD20 on mature B lymphocytes can be successful in severe recalcitrant forms of scleritis [9, 11, 12]. This potential effectiveness is supported by 1 study [19] of a small number of eyes enucleated because of severe necrotizing auto-immune scleritis that showed CD20 positive cells along with plasma cells as major components of the inflammatory infiltrate. Finally, a case-report of a patient with nodular scleritis illustrates that adalimumab, a humanized monoclonal antibody against soluble and membrane-bound TNF-α, may be effective as well [13].

Within the present cohort, scleritis seems to be divided into 2 variants. A mild form which is responding well to NSAIDs and a more severe or recalcitrant variant that required other types of treatment. Low-dose corticosteroids as monotherapy seemed to be effective in only a minority of these patients. Because most patients in the severe group needed steroid-sparing immunosuppressive drugs, the threshold to start these should be low. Globally, for each steroid-sparing immunosuppressive drug, treatment success was achieved approximately half of the patients. Azathioprine seems to be an exception because this drug was much less effective in the present study.

Assessing the severity of scleritis at an early stage is important for an adequate choice of treatment regimen. Within this patient group necrotizing scleritis, male gender, a longer period of complaints at presentation, systemic disease, and bilateral disease at any time indicated a worse prognosis. By multivariate regression analysis, bilateral disease was the strongest predictor of worse prognosis. Patients with these characteristics at presentation had more loss of visual acuity, longer disease duration and were more often treated with steroid sparing immunosuppressive medication. Risk factors for visual loss or prolonged treatment in the literature include necrotizing or posterior scleritis [31], underlying systemic disease [15], corneal involvement [32], positive results for c-ANCA [20], a combination of anterior and posterior scleritis [16] and a posterior scleritis at an older age than 50 years [16]. With regard to necrotizing scleritis and systemic disease, the present results were in agreement with dose reported in the literature. Most of these factors are easy to observ at presentation or during the course of the disease and contribute to an early recognition of a more severe form of scleritis. In contrast, the scleritis scoring system proposed by McCluskey and Wakefield [4] did not contribute to estimating the severity of scleritis in the current patients.

However, the results of the current study are limited by the fact that the study was retrospective, the numbers of patients were small in some subgroups, there was a large variability in follow up and the inclusion period was relatively long [17, 18]. Also, the Snellen visual acuities were not obtained according to a standardized protocol and our study was conducted in 2 subspecialty clinics at university hospitals and therefore this population does not represent the total spectrum of scleritis. Regarding treatment; there is a bias towards personal experience and preferences of the ophthalmologists of the two university hospital centers and there is an unknown influence on treatment of the health insurance politics in the Netherlands. Despite this, the authors believe that they can make contributions and recommendations for the improvement of care for scleritis patients by sharing our treatment experiences, indicating prognostic factors and advising on steps to optimize treatment regimens.

In conclusion, these data shows that scleritis often is a severe, vision threatening, and chronic eye disease. Patients with a mild form of scleritis in most cases are treated adequately with oral NSAIDs. Patients with more severe or recalcitrant forms of scleritis can benefit from a more aggressive treatment strategy. Clinical features indicating a more severe form of scleritis make a fast recognition of the disease possible. Adequate treatment based on the severity of the scleritis and a timely switch to steroid-sparing immunosuppressive drugs can reduce total treatment time. Using an appropriate MTX dose-escalation scheme and an earlier switch to subcutaneous administration seems advisable in patients with non-infectious recalcitrant scleritis. Azathioprine should be avoided in patients with scleritis. After MTX failure, MMF is a good option as a secondary steroid-sparing immunosuppressive drug. Tumor necrosis factor-α antagonists may be a viable option for patients with noninfectious, recalcitrant scleritis who are not responding to MTX or MMF.

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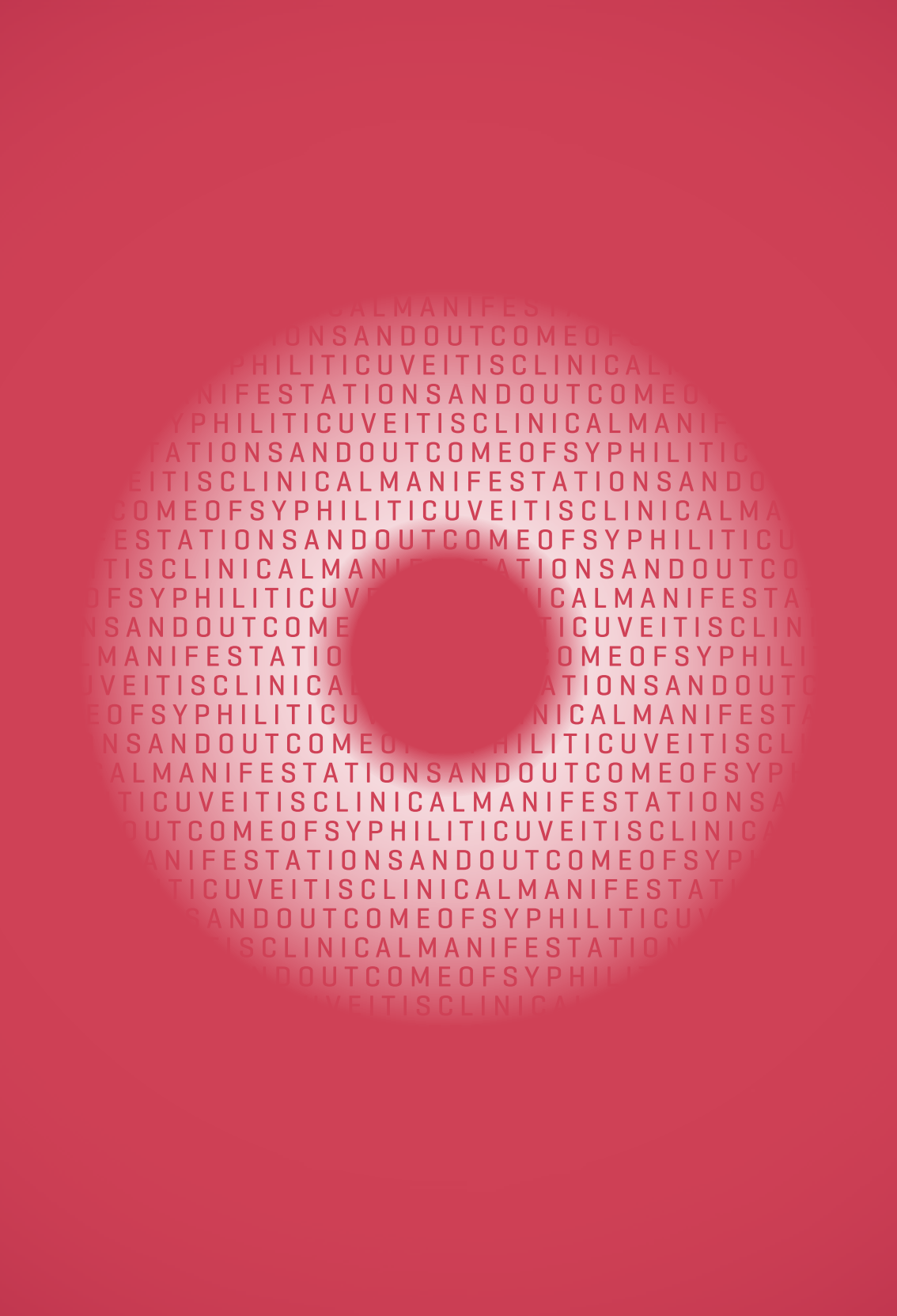
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3 CLINICAL MANIFESTATIONS AND OUTCOME OF SYPHILITIC UVEITIS

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Invest Ophthalmol Vis Sci. 2016 Feb;57(2):404-11

ABSTRACT

Purpose: To analyze visual outcome, effectiveness of various modes of antibiotic treatment and prognostic factors in patients with serologically proven syphilitic uveitis.

Methods: The clinical records of 85 patients (139 eyes) diagnosed with syphilitic uveitis between 1984 and 2013 at tertiary centers in the Netherlands were retrospectively analyzed.

Results: Mean age was 47 years (range 27 – 73), 82.4% were male. HIV positivity was found in 28 (35.9 %) patients, 13 were newly diagnosed. Most patients had pan (45.9%) or posterior (31.8%) uveitis. On average, LogMAR VA improved significantly from 0.55 at the start of syphilis treatment to 0.34 at 1 month and to 0.27 at 6 months follow up. Most patients (86.7%) reached disease remission. No differences in efficacy between the various treatment regimens were found. A high LogMAR VA at the start of syphilis treatment and a treatment delay of more than 12 weeks were prognostic for a high LogMAR VA at six months follow up. Chronicity was not related to any form of treatment, HIV status or VDRL test outcome.

Conclusion: In this large cohort of 85 patients with syphilitic uveitis, visual outcomes were favorable in the majority of cases. Visual outcome was dependent on VA at the start of syphilis treatment and treatment delay.

INTRODUCTION

Syphilis is caused by an infection with the bacterium Treponema pallidum (T. pallidum) and classified as acquired or congenital. As with other spirochete infections, the clinical course of acquired untreated syphilis can be divided into four different stages depending on the clinical manifestations[1]. Syphilitic uveitis can occur in all stages except in the primary stage.

Different tests are available for the diagnosis and staging of syphilis. These include the so-called nonspecific tests like the VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin), which quantify the amount of serum anticardiolipin antibodies by flocculation and T. pallidum specific tests like the FTA-ABS (Fluorescent treponemal antibody absorption test), TPPA (Treponema pallidum particle agglutination) and TPHA (Treponema pallidum haemagglutination assay), which measure the amount of serum antibodies specifically directed against treponemal antigens[1]. As was shown by Grange et al[2], newer PCR-based techniques have very low sensitivity to detect syphilis in blood, and thus cannot replace the above-mentioned serological tests.

The clinical presentation of ocular syphilis has been described in many publications. It has been dubbed "The Great Imitator" as it can mimic a wide range of ocular disorders. The most common presentation of ocular syphilis is uveitis. Before 1940, syphilis was the second cause of uveitis after tuberculosis. With the introduction of penicillin and improved diagnostics, syphilitic uveitis is a rare disease nowadays, accounting for 1 to 2% of all uveitis patients[3]. However, the outcomes of the different serologic tests for syphilis can be confusing, the optimal treatment of syphilitic uveitis is debatable and it is unknown which factors will determine visual prognosis.

To contribute to clarification of these aspects, we retrospectively evaluated visual outcomes in 85 patients with syphilitic uveitis. Specifically, factors that correlated with a worse visual prognosis or a chronic disease course were investigated.

PATIENTS AND METHODS

Patients with a confirmed diagnosis of syphilitic uveitis between 1984 and 2013 at the University Medical Centers of Leiden (n=12), Groningen (n=19), Utrecht (n=33), the VU University Medical Center Amsterdam (n=3) and the Rotterdam Eye Hospital (n=18) were included. The diagnosis of syphilitic uveitis was made in uveitis patients with positive results for specific anti T. pallidum serologic tests (i.e. a positive TPPA or TPHA and/or a positive FTA-ABS test) and agreement on the diagnosis syphilitic uveitis between ophthalmologist, dermatologist,

infectious disease specialist and neurologist. In the above centers, serologic testing for syphilis is part of the work-up in uveitis of unknown cause[4]. This work-up depends on the clinical presentation of the uveitis and may include blood tests (e.g. ESR, CRP, Hb, Ht, erythrocyte, thrombocyte and leukocyte counts, leukocyte differential, kreatinin, sodium, potassium, calcium, albumin, liver transaminases, angiotensin converting enzyme, auto-antibodies, tests for tuberculosis and chest X-rays. Additional tests may be ordered in special situations (e.g. anterior chamber fluid tests for infectious uveitis). (Uveitis Guidelines Dutch Opthalmic Society, 2007)[4]. However, since all these centers are tertiary referral centers, patients are often referred by ophthalmologists working in general practices. A systematic work-up for uveitis has not always been performed prior to referral. Medical records were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki and the study design was evaluated by the Medical Ethical Committee of the University Medical Center of Groningen who ruled that approval was not required for this study.

All participating centers collect data on uveitis patients in a database. However, the inclusion of patients started at different time points at the different centers. Therefore, the inclusion period varied per center (years are given between brackets): Leiden University Medical Center (1985 to 2008), University Medical Center Groningen (2001 to 2013), University Medical Center Utrecht (1991 to 2011), VU University Medical Center Amsterdam (2009 to 2012) and the Rotterdam Eye Hospital (1996 to 2010).

The following data were recorded on an anonymized standard entry form: sex, age at the start of syphilis treatment, race, affected eye(s), interval between the date of onset of uveitis symptoms and the date of final diagnosis of syphilitic uveitis and initiation of anti-syphilis treatment, laboratory data including HIV status and the results of various serologic tests for syphilis, the results of cerebrospinal fluid analyses, classification of the uveitis based upon standardization of uveitis nomenclature (SUN) criteria[5], various clinical features, treatment modalities, visual acuity in logarithm of the minimal angle of resolution units (LogMAR) at the start of syphilis treatment, and at one and six months follow-up. The Snellen VA was converted to LogMAR VA for calculations. Visual acuity at one and six months was analyzed in relation to type of uveitis, treatment before syphilis treatment, interval between uveitis and syphilis treatment, administration route of syphilis treatment, HIV-status and immunosuppressive treatment during syphilis treatment.

Uveitis was classified as anterior, intermediate, posterior or panuveitis. The presence of cystoid macular edema (CME) was confirmed by fluorescein angiography (FA) or optical coherence tomography (OCT). Retinitis, retinal ischemia and papillitis were diagnosed by FA. Serous retinal detachments were

diagnosed by fundoscopy or ultrasound (US). Fundoscopically observed retinal hemorrhages and retinal vasculitis were recorded. Chronic uveitis was defined as persistent uveitis with relapse within 3 months after discontinuing treatment [5] or as an active uveitis at 6 months follow up.

The following treatment regimens were included: 1. Benzyl penicillin 0.15 million units/kg/day intravenously for 14 days, 2. Procaine penicillin 1.2–2.4 million units intra-muscularly during 10–17 days, and 3. Oral doxycycline 200 mg twice per day for 28 days or ceftriaxone intravenously 2 g/day for 14 days. Patients were divided into three groups based on the time interval between presentation of uveitis and the start of syphilis treatment. The first group received treatment within 4 weeks after presentation of the uveitis, the second was treated within four to twelve weeks after presentation and the third started treatment after a twelve week interval.

Adjunctive treatment with corticosteroids (eye drops, peri-ocular injections and systemic) and other immunosuppressives (systemic) was recorded. For statistical analyses, three groups were made. 1. Patients without adjunctive treatment with steroids. 2. Patients who received adjunctive treatment with steroid eye drops. 3. A combined group of patients (n=36) who received adjunctive treatment with subconjunctival (n=4) or systemic corticosteroids (n=32).

Statistical analysis was performed by SPSS® software version 20 (SPSS, Inc., Chicago, IL). A $P < 0.05$ was considered statistically significant. Analysis of VA improvement was done by comparing VA at the start of syphilis treatment to that at one and six months by Friedman ANOVA with post hoc Wilcoxon signed-rank test and Bonferroni correction. The Mann-Whitney test was used to test for statistical differences in VA at one and six months between the groups that were treated with local or systemic corticosteroids and between HIV negative and positive patients. The chi-squared test was used to test for relationships between HIV status and anatomical location of the uveitis or cerebrospinal fluid abnormalities, respectively. A multiple linear regression model was used to assess the weight and value of the prognostic factors for visual outcome at six months.

RESULTS

Of the 89 patients classified as having syphilitic uveitis, a cohort of 85 patients could be evaluated in detail, while 4 patients were excluded because of lack of documentation. Patients' characteristics are summarized in Table 1. As shown, only patients with a positive TPHA or TPPA test were included. In addition, VDRL testing was done in all patients, 69 (81.2%) of whom were positive. Of the 16 VDRL negative patients one patient was HIV positive. Two patients had a documented

re-infection, they were both VDRL positive. FTA-Abs tests were positive in all 43 tested patients. The majority of patients (82.4%) were male and most (63.5%) had bilateral disease. Lumbar punctures had been performed in 62 (72.9%) patients (Table 1). Cerebrospinal fluid (CSF) tested positive for TPHA or TPPA in 33/57 (57.9%) patients, VDRL in 12/31 (38.7%) and FTA-Abs in 4 out of 6 tested patients. In 28 (35.9%) patients, a HIV co-infection was present. Of these, 15 (53.6%) had previously been diagnosed with HIV, and 13 (46.4%) were newly identified. No statistically significant relationship was found between anatomical location of the uveitis, HIV status and cerebrospinal fluid abnormalities.

Ocular features are shown in Table 2. In case of posterior and panuveitis, optic nerve and retinal involvement and vitritis probably explain the low VA at presentation. Visual field defects at any moment during follow up were found in 44 out of 52 (84.6%) tested eyes. These were predominantly eyes with posterior (n=14, 31.8%) or panuveitis (n=22, 50%).

In Table 3 and 4, the LogMAR VA per eye at the start of syphilis treatment and at 1 and 6 months is shown. On average, a statistically significant improvement in VA was observed at 1 and 6 months as compared to VA at start of syphilis treatment.

Most patients were treated with intravenous (IV) benzyl penicillin G (n=55, 64.7%) or ceftriaxone (n=2, 2.4%) for 2 weeks (Table 4). Intra muscular (IM) treatment with procaine penicillin was given in 15 (17.6%) patients, 5 (5.9%) patients were treated with oral antibiotics (doxycycline in all cases) and 8 (9.4%) patients were treated with a combination of IV, IM and oral treatment.

Table 1. Patient Characteristics (N=patients)

Syphilitic uveitis	**N (%)**
Mean age (range)	46.96 (27 – 73)
Male	70/85 (82.4%)
Bilateral	54/85 (63.5%)
Etnicity	
Caucasian	67/85 (78.8%)
Other*	18/85 (21.2%)
Serological tests for Syphilis	
TPHA/TPPA positive	85/85 (100%)
VDRL positive	69/85 (81.2%)
FTA-Abs positive	43/43 (100%)
Lumbar puncture findings	
Performed lumbar punctures	62/85 (72.9%)
Positive TPHA/TPPA	33/57 (57.9%)
Positive VDRL	12/31 (38.7%)
Positive FTA-Abs	4/6 (66.7%)
HIV status	
HIV positive	28/78 (35.9%)
Already known	15/28 (53.6%)
Newly diagnosed	13/28 (46.4%)
Interval uveitis and syphilis	
< 4 weeks	36/85(42.4%)
4 – 12 weeks	16/85 (18.8%)
>12 weeks	33/85 (38.8%)
Administration route antibiotics for syphilis treatment	85/85 (100%)
Intra-venous	57/85 (67.1%)
Intra-muscular	15/85 (17.6%)
Oral	5/85 (5.9%)
Combination of the above	8/85 (9.4%)

The fraction (x/y) displays the number of patients with a specific characteristic (x) in relation to the total number of patients evaluated (y). * Surinam Blacks n=7, African Americans n=2, Asians n=7, Surinam Indians=2

Table 2. Ocular features

	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	Sclero-uveitis	Total (n)
Number of patients	14	2	27	39	3	85
Visual acuity at presentation						
> 20/50	10	2	8	15	0	35
20/200 – 20/50	2	0	7	13	3	25
>NLP[1] – 20/200	2	0	12	11	0	25
NLP	0	0	0	0	0	0
Number of affected eyes	22	4	42	66	5	139
Vitritis	3	4	18	55	5	85
Cystoid macular edema	2	0	9	20	1	32
Retinitis	0	0	31	50	5	86
Retinal ischemia	0	0	10	20	1	31
Retinal hemorrhages	0	0	14	22	4	40
Retinal vasculitis	0	0	17	30	3	50
Papillitis	0	2	31	39	2	74

[1] NLP: no light perception

Table 3. VA, uveitis type and HIV-status (Log MAR acuity per eye, n=eyes)

	VA at start of syphilis	VA at 1 month	VA at 6 months	P 0 – 1 month*	P 0 – 6 months §	P 1 – 6 months λ
Total group (N=patients)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6)	(117/139) **0.27** (SD 0.51)	**< 0.001**	**< 0.001**	**< 0.001**
Type of uveitis						
Anterior uveitis (N=14)	(22/139) **0.32** (SD 0.5)	(22/134) **0.3** (SD 0.63)	(16/117) **0.33** (SD 0.73)	NS	NS¶ (0.021)	**0.003**
Intermediate uveitis (N=2)	(4/139) **0.06** (SD 0.16)	(4/134) **0.009** (SD 0.1)	(2/117) **0.097**	NS	NS	NS
Posterior uveitis (N=27)	(42/139) **0.61** (SD 0.60)	(40/134) **0.33** (SD 0.52)	(39/117) **0.31** (SD 0.56)	**0.01**	**0.016**	NS
Pan uveitis (N=39)	(66/139) **0.56** (SD 0.67)	(64/134) **0.39** (SD 0.67)	(56/117) **0.26** (SD 0.49)	**< 0.001**	**< 0.001**	**0.003**
Sclero-uveitis (N=3)	(5/139) **1.4** (SD 1.1)	(4/134) **0.18** (SD 0.3)	(4/117) **0.1** (SD 0.21)	NS	NS	NS
HIV						
Positive N=28#	(48/139) **0.56** (SD 0.67)	(48/134) **0.28** (SD 0.57)	(37/117) **0.26** (SD 0.52)	**< 0.001**	**0.001**	NS¶ (0.029)
Negative N=50#	(91/139) **0.55** (SD 0.65)	(86/134) **0.37** (SD 0.61)	(80/117) **0.27** (SD 0.5)	**< 0.001**	**< 0.001**	**< 0.001**

All uveitic eyes were included in this analysis. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of eyes evaluated (y).To correct for the bias of systemic treatment in bilateral versus unilateral disease, Table 5 was added. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. λ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months. # No significant difference in VA outcome between the two groups (Mann-Whitney test). ¶ After Bonferroni correction a P ≤ 0.0167 (0.05/3) is required.

Only in patients treated by IV antibiotics, a statistically significant VA improvement at 6 months (as compared to VA at start of treatment) was seen (Table 4). Patients treated with antibiotics by different routes of administration, also had VA improvement at 6 months, but this was not statistically significant (Table 4). Sixty-seven patients (78.8 %) received systemic, subconjunctival or

Table 4. VA and treatment (Log MAR acuity per eye, n=eyes)

	VA at start of syphilis treatment	VA at 1 month	VA at 6 months	P 0 – 1 month*	P 0 – 6 months §	P 1 – 6 months ^λ
Total group (N=patients)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6)	(117/139) **0.27** (SD 0.51)	**< 0.001**	**< 0.001**	**< 0.001**
Treatment before syphilitic treatment						
Missing data	11/139	11/134	9/117			
No treatment (N=41)	(69/128) **0.51** (SD 0.6)	(67/123) **0. 29** (SD 0.52)	(62/108) 0.**29** (SD 0.61)	**< 0.001**	**0.002**	**0.010**
Corticosteroids and other immunosuppressives N=14	(24/128) **0.51** (SD 0.64)	(22/123) **0.42** (SD 0.78)	(20/108) **0.28** (SD 0.47)	NS¶ (0.036)	**0.011**§	NS¶ (0.043)
Other treatment (not adequate) N=23	(35/128) **0.69** (SD 0.76)	(34/123) **0.42** (SD 0.68)	(26/108) **0.20** (SD 0.38)	**0.006**)	**<0.001**	**0.002**
Interval uveitis and syphilis treatment						
< 4 weeks N=36	(56/139) **0.59** (SD 0.73)	(55/134) **0.34** (SD 0.68)	(43/117) **0.20** (SD 0.42)	**< 0.001**	**< 0.001**	**< 0.001**
4 – 12 weeks N=16	(29/139) **0.45** (SD 0.58)	(25/134) **0.22** (SD 0.39)	(22/117) **0.09** (SD 0.22)	**0.012**	**< 0.001**	**< 0.001**
>12 weeks N=33	(54/139) **0.57** (SD 0.63)	(54/134) **0.39** (SD 0.6)	(52/117) **0.40** (SD 0.62)	**0.008**	NS¶ (0.022)	NS
Administration route syphilis treatment						
Intra-venous N=57	(99/139) **0.53** (SD 0.61)	(96/134) **0.30** (SD 0.59)	(86/117) **0.25** (SD 0.52)	**< 0.001**	**< 0.001**	**0.002**
Intra-muscular N=15	(20/139) **0.51** (SD 0.81)	(18/134) **0.4** (SD 0.63)	(16/117) **0.38** (SD 0.64)	NS	NS	NS¶
Oral N=5	(7/139) **0.52** (SD 0.74)	(7/134) **0.51** (SD 0.74)	(7/117) **0.18** (SD 0.28)	NS	NS¶ (0.043)	NS¶ (0.028)
Combination of the above N=8	(13/139) **0.78** (SD 0.75)	(13/134)**0.49** (SD 0.55)	(8/117) **0.43** (SD 0.68)	NS	NS¶ (0.018)	NS¶ (0.046)
Immunosuppressive treatment during syphilis treatment						
Missing data	3/139	1/134	1/117			
Oral or subconjunctival corticosteroids# N=36	(63/136) **0.65** (SD0.65)	(60/133) **0.33** (SD 0.58)	(58/116) **0.28** (SD 0.56)	**< 0.001**	**< 0.001**	**0.003**
Corticosteroid eye drops# N=31	(46/136) **0.44** (SD 0.58)	(46/133) **0.41** (SD 0.72)	(37/116) **0.28** (SD 0.55)	NS	**0.001**	**0.008**
No corticosteroids N=16	(27/136) **0.48** (SD0.7)	(27/133) **0.24** (SD 0.38)	(21/116) **0.25** (SD 0.45)	NS¶ (0.037)	NS¶ (0.035)	NS¶ (0.062)

All uveitic eyes were included in this analysis. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of eyes evaluated (y).To correct for the bias of systemic treatment in bilateral versus unilateral disease, Table 5 was added. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. ^λ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months. # No significant difference in VA outcome between the two groups (Mann-Whitney test). ¶ After Bonferroni correction a $P \leq 0.0167$ (0.05/3) is required.

local steroids next to antibiotic treatment. No statistically significant difference in VA at six months was found between patients who had versus those who had not received any adjunctive treatment with systemic or local steroids (p=0.691). No cases of Jarisch-Herxheimer reaction were reported.

Table 5 displays the course of the disease after treatment. Ten (13.5 %) patients developed chronic uveitis. Chronicity was not related to the duration of treatment delay, any form of treatment or outcome of VDRL testing.

Table 5. Administration route syphilis treatment (N=patients)

Administration route syphilis treatment	N (%)	Remission at 6 months[#]	Chronic at 6 months
Total	85/85	65/75 (86.7%)	10/75 (13.3%)
Intra-venous	57/85 (67.1%)	44/57(77.2%)	7/57 (12.2 %)
Intra-muscular	15/85 (17.6%)	11/15 (73.3)	2/15 (13.3 %)
Oral	5/85 (5.9%)	5/5	0
Combination of the above	8/85 (9.4%)	5/8 (62.5%)	1/8 (12.5%)

[#] In 10 patients data regarding disease status at 6 months was missing.

With Friedman ANOVA statistical analysis, we evaluated VA outcomes at one and six months when compared to VA at the start of syphilis treatment. Delayed treatment in itself was associated with less VA improvement at six months. Whether patients had received any form of treatment not specifically directed at syphilis as compared to no treatment prior to the start of specific treatment directed at syphilis, did not seem to affect VA outcomes at 1 and 6 months (Table 4). Prior treatment regimens differed and consisted of antivirals (n=10) or antibiotics / anti-toxoplasmosis drugs (n=13).

By using a multivariate linear regression model, we analyzed which factors were associated with the outcome variable LogMAR VA at 6 months. Within this model, we took into account: the type of uveitis, delay between onset of uveitis and treatment, bilateral disease, ethnicity, VDRL test results, route of administration of treatment, HIV-positivity, treatment before syphilis treatment, the use of corticosteroids or other steroid-sparing immunosuppressive drugs and VA at the start of syphilis treatment. Regarding VDRL status, the statistical analysis in this regression model was done in two ways. The first analysis was done with the VDRL negative versus the VDRL positive patients. The second analysis was done with the VDRL positive patients versus the combined VDRL negative patients and patients with a low VDRL-titer (below 1:8). With this model, we found that a lower VA at the start of syphilis treatment (P<0.001) and a delay of more than 12 weeks between presentation and treatment for syphilis (P=0.038), were associated with a statistically significantly worse visual outcome at 6 months. These two variables explain 34.6% (R Square 0.346) of the variance in VA outcomes at 6 months.

Table 6. Best eye analysis1 (Log MAR acuity per eye)

Ocular syphilis	VA at presentation	VA at 1 month	VA at 6 months	VA difference 1 and 6 months ‡
All eyes (n=139)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6) P=0.001*	(117/139) **0.27** (SD 0.51) P=<0.001§	P=<0.001
Unilateral eyes (n=31)	(31/31) **0.71** (SD 0.77)	(31/31) **0.4** (SD 0.55) P=0.003*	(26/31) **0.25** (SD 0.4) P=<0.001§	P=0.002
Bilateral best eye and unilateral eyes (n=85)	(85/85) **0.39** (SD 0.58)	(83/85) **0.22** (SD 0.47) P=<0.001*	72/85 **0.15** (SD 0.33) P=<0.001§	P=<0.001

To correct for the bias of systemic therapy in bilateral versus unilateral disease, we performed VA analyses at the various time points for all eyes, unilateral eyes only, and bilateral best eyes plus unilateral eyes. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of evaluated eyes (y).The results of all analyses show a significant improvement of VA between all-time points and in all analyzed groups. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. ‡ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months.

Table 7. Characteristics of 6 patients (10 eyes) with visual loss at 6 months.

Patient	No eyes	Type of uveitis	VA at presentation	VA at 1 month	VA at 6 months	HIV	Cause of visual loss	Previous immunosupressives	Treatment within 4 weeks	Administration route
1	2	posterior	0.2	NLP	NLP	-	Ischemic optic neuropathy	Oral corticosteroids	No	IV
			0.2	NLP	NLP					
2	2	posterior	1.2	0.8	0.3	-	Optic neuropathy	No	No	IV
			FC	HM	HM		Sub retinal fibrosis			
3	2	pan	0.8	HM	0.1	+	Retinal detachment	Oral corticosteroids and cyclosporine	No	IV
			HM	HM	0.1		glaucoma		No	
4	1	posterior	*1.2*	*1.2*	*1.2*	-		No	No	IV
			0.1	FC	FC		Sub retinal fibrosis			
5	1	sclero-uveitis	*0.5*	*0.8*	*0.8*	unknown	Optic neuropathy	No	Yes	IV
			HM	NLP	NLP		Sub retinal fibrosis			
6	2	anterior	0.8	0.25	0.25	-		No	No	IM
			0.4	HM	HM		hypopyon			

Ten eyes of 6 patients with bilateral uveitis lost VA during follow-up. (The data of the two eyes that improved are given in italics). VA = Visual acuity (Snellen), IV = Intra venous, IM = Intra muscular, FC = Finger counting, HM = Hand motion, NLP = No light perception.

To correct for the possible bias of systemic treatment in a mixed population of bilateral and unilateral disease we took bilateral disease into account in the regression model and we added Table 6. Bilateral disease did not influence the visual outcome at 6 months (P=0.216).

Table 7 shows the characteristics of the 6 patients (10 eyes) with visual loss at 6 months. Posterior uveitis was the predominant type of uveitis associated with visual loss. Optic neuropathy, subretinal fibrosis, retinal detachment and glaucoma were the main causes of severely reduced VA in these patients. In one patient with hand motion VA, the posterior segment could not be evaluated due to severe persistent anterior segment inflammation (hypopyon) (This patient refused intensive local treatment).

DISCUSSION

Within this cohort of 85 patients with serologically proven syphilitic uveitis , the overall visual prognosis was good if timely and adequate therapy was given. High LogMAR VA (low Snellen VA) outcomes were associated with a treatment delay of more than 12 weeks, and high LogMAR VA at the start of syphilis treatment. A statistically significant improvement of VA at 1 and 6 months as compared to that at the start of syphilis treatment, was observed in patients treated with IV antibiotics, and in those that received adjunct corticosteroids. Absolute values of LogMAR VA at 6 months were not associated with the route of administration of antibiotics, treatment with corticosteroids and HIV status. The majority of patients had one uveitis episode, but chronic uveitis developed in 13.5%. None of the evaluated factors was associated with a chronic course.

Overall, a good visual prognosis in our study is supported by the finding that the 117 eyes included in the per eye analysis showed a statistically significant improvement at one and six months follow up. Also, 16 of the 22 eyes (72.7%) with missing data at 6 months had a Snellen VA above 20/32 (LogMAR 0.2) at 1 month follow up. Therefore, we may assume an even more favorable prognosis than that presented in our tables. An overall good visual prognosis in syphilitic uveitis such as found in this large cohort, confirms previous studies [6-11]. In our study, a higher LogMAR VA at the start of syphilis treatment and a delay of more than 12 weeks between the first presentation of uveitis and treatment for syphilis, were associated with a statistically significantly higher LogMAR VA at 6 months. Possible reasons for diagnostic delay include patients' and doctors' delay. It is hard to reduce the former, whereas the latter can be minimized by following the general advice to test for syphilis in patients with uveitis of unknown origin [1, 12, 13].

Treatment outcome

Probably, delayed treatment is associated with irreversible structural damage [1, 7, 14, 15]. This is supported by the association between high LogMAR VA at the start of syphilis treatment and at 6 months. Worsening of VA during follow up occurred in ten eyes and was associated with structural damage to the optic disc and retina. In our study, the majority of patients were treated with intravenous penicillin (Table 4). Smaller numbers of patients were treated with intramuscular or oral antibiotics. These different treatment modalities were not prognostic for a higher LogMAR VA at 6 months.

Previous studies on prognostic factors in ocular syphilis [6, 16, 17] showed no difference in visual outcome when comparing the "classic" regimen of intravenous penicillin with other antibiotics. But, these studies [6, 16, 17] were all in small groups, with different kind of antibiotics and therefore results should be interpreted cautiously.

Corticosteroids

Another finding in our study is that patients who received local, subconjunctival or systemic corticosteroids next to antibiotic treatment for syphilis had on average a statistically significant improvement in VA at 1 and 6 months, when compared to VA at the start of syphilis treatment. The absence of a statistically significant difference between patients treated with additional oral steroids or steroid injections versus those not treated in this way, seems to indicate that additional steroids may be ineffective. However, the fact that mean LogMAR VA at the start of syphilis treatment was higher in patients receiving additional oral steroids or steroid injections than in patients not receiving this (Table 4), indicates that adjunct corticosteroid treatment may have been preferably given to the more severe cases. Since LogMAR VA outcomes in these possibly more severe cases are similar to outcomes in the probably less severe groups (Table 4), a beneficial effect of adjunct corticosteroid treatment cannot be excluded. Some authors have reported on their clinical experience with corticosteroids in ocular syphilis [18, 19] but on a smaller scale and not at set time points. Previous studies advised local corticosteroids in case of interstitial keratitis or anterior uveitis [14, 20] and systemic corticosteroids in case of profound visual loss, posterior uveitis [21], scleritis, and optic neuritis [14, 20]. Because of our results and recommendations in the literature, we suggest considering adding corticosteroids to antibiotic treatment in all cases of syphilitic uveitis. The use of oral corticosteroids is also considered beneficial in preventing a Jarisch–Herxheimer reaction [20, 22]. The use of corticosteroids without antibiotic treatment, though not associated with worse VA outcomes at 6 months in our study, may aggravate syphilitic uveitis. Zamani and Garfinkel [23] published a case report on a patient who developed yellow placoid chorioretinal lesions during treatment with oral corticosteroids, which disappeared after their discontinuation.

HIV

In our study, HIV positivity was found in 28 patients, 13 of whom were newly diagnosed. This re-emphasizes the risk of co-infection with other sexually transmitted diseases in this patient group, and the desirability to test for HIV in case of ocular syphilis. Previously, HIV-positivity has been associated with a worse visual outcome in syphilitic uveitis, a finding we and other recent studies [9-11, 24, 25] could not confirm. Also, previous studies described that HIV-positive patients tended to have a higher proportion of posterior and panuveitis and neurosyphilis than HIV-negative patients. In contrast, we did not find statistically significant associations between HIV- positivity, anatomical location of the uveitis and CSF abnormalities. Differences between our outcomes and those in previous studies may be due to an improved immune-status of HIV-positive patients because of highly active antiretroviral therapy (HAART) [26, 27]. In line with this, current IUSTI guidelines [1, 12, 13] state that HIV co-infected syphilitic patients should be treated as immunocompetent patients, except for those who have CD4+ cell counts of less than or equal to 350/µl.

Clinical presentation

Our study confirms previous reports [6, 7, 16, 28, 29] that ocular syphilis occurs predominantly in men. Further, it confirms that syphilitic uveitis is a variable condition with a high diversity of clinical features. It can be uni- or bilateral, all anatomical locations may be affected, and it may run an acute or chronic course. In our study, bilateral uveitis was seen in 63.5%, whereas posterior (n=27, 31.8%)) and panuveitis (n=39, 45.9%) were far more often present than anterior uveitis (n=14, 16.5%). This is in line with recent papers [6, 7, 16, 24], but it differs from some older studies that observed uveitis to be located mainly anteriorly [30, 31].

VDRL test outcome

VDRL test results give some information on the duration and activity of the infection and they can be used to monitor the response to treatment. The interpretation of the VDRL test is sometimes difficult and debatable. A VDRL test becomes positive 4 to 5 weeks after infection, but it can sometimes be negative due to the prozone phenomenon[1]. Next to that, in 20 - 30% of the patients the test becomes negative over time [32]. Therefore, a negative VDRL test result does not rule out the diagnosis of syphilitic uveitis[10]. A previous study reported that HIV positivity may be associated with higher than expected VDRL serologic titers, false-negative serologic results and delayed appearance of sero-reactivity [32]. These findings were not confirmed within our study. Also, we did not observe an effect of VDRL test outcome on VA at 6 months in the multivariate linear regression model. Neither did we find a difference in chronicity at 6 months between VDRL-negative or positive patients.

Antibiotic Treatment

According to the European guidelines, the gold standard for the treatment of syphilitic uveitis is intravenous (IV) benzyl penicillin 12–24 million units daily, given in 3–4 million units doses every four hours for 10–21 days [1, 12, 13]. In special situations (pregnancy, allergy or refusal of intravenous treatment), oral or intramuscular treatment can be considered. Improvement in VA at 1 and 6 months was seen in all groups of patients independent of the route of administration of antibiotics. Based upon the multiple linear regression model , the group of patients treated with IV penicillin, showed a tendency towards a somewhat better VA result. The absence of a statistically significant difference in this model may probably be explained by the modest sizes of the non IV treated groups. A similar argument may apply to the absence of an effect of route of administration on the development of chronic uveitis. At present, the results of our study support the current guidelines on treatment for ocular syphilis.

Strengths and limitations of the study

The strengths of this study are its relatively large study population, the systematic way in which data were collected, and its adherence to the SUN classification system and guidelines for publications. The limitations of this study are its retrospective nature, and its long inclusion period. The latter may theoretically have influenced treatment strategies. However, the mainstay of syphilis treatment is penicillin, and this has not changed over the past decades. Some statistically significant relations may have been missed because of small numbers of patients in some subgroups. Also, the study was conducted in tertiary uveitis centers, and therefore, this population may not represent the total spectrum of syphilitic uveitis. Personal experience and preferences of ophthalmologists may have influenced their choice of treatment. Despite this, we feel that the study results can contribute to optimum care for patients with syphilitic uveitis.

CONCLUSION

Overall, VA outcomes in syphilitic uveitis are good. A low VA at the start of syphilis treatment and treatment delay of more than 12 weeks results in a less favorable visual prognosis. To shorten this delay, low threshold testing for syphilis should be done in uveitis of unknown cause. Intravenous benzyl penicillin is an effective treatment for syphilitic uveitis. It is not clear whether adjunct steroid treatment is beneficial. Structural damage to the optic nerve and retina are the main causes of permanent visual loss.

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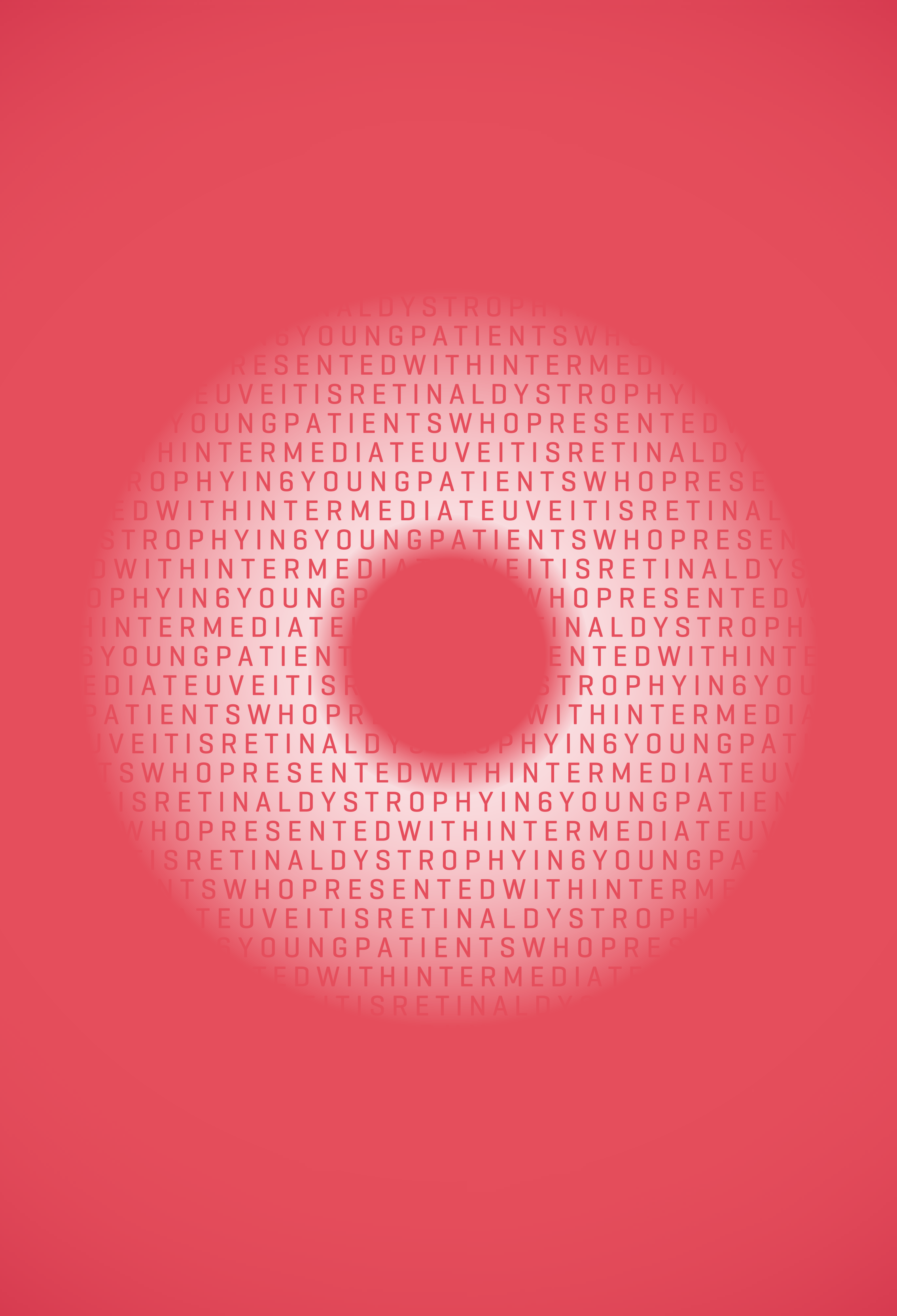
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4

RETINAL DYSTROPHY IN 6 YOUNG PATIENTS WHO PRESENTED WITH INTERMEDIATE UVEITIS

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Ophthalmology. 2016 Sep;123(9):2043-6.

Inherited retinal dystrophies (RD) comprise a clinically and genetically heterogeneous group of inherited diseases characterized by progressive rod and cone dysfunction and degeneration. Intermediate uveitis (IU) is a clinical diagnosis characterized by bilateral intraocular inflammation located primarily in the vitreous and pars plana. IU is the second most common uveitis entity among children. Most young patients with IU do not present with any apparent underlying disease.[1] IU is frequently complicated by cystoid macular edema (CME), which may also occur in RD.

We describe six patients initially diagnosed with IU who visited the outpatient uveitis clinics of three University Medical Centers at Utrecht, Groningen and Amsterdam between 2006 and 2015. During the course of the disease, these patients were diagnosed with RD.

At presentation, age of the patients ranged from 5 to 22 years. Five patients had a negative family history for consanguinity or retinal or immunological disease and for one patient (patient 3, Table 1) it was unknown. They all had subnormal vision (range: 20/25 – 20/50 Snellen equivalent) and one patient complained of nyctalopia. Slit-lamp examination revealed minimal or no anterior segment inflammation and 1+ to 3+ cells with mild to moderate haze in the vitreous. Funduscopy showed CME in all patients and several white peripheral lesions in one patient and some pigment deposits in another patient. None of the six patients had waxy disc pallor or the typically pigment changes seen in RD.

Visual field (VF) testing was performed in all patients at different time points due to referral delay by general ophthalmologists. VF of all patients showed various degrees of relative (mid-) peripheral defects (n= 3) or ring scotoma (n=3) 1 to 7 years after onset of complaints. Optical coherence tomography (OCT) showed CME on OCT in all patients with foveal thickness ranging from 206 μm (but cysts present) to 651 μm (Table 1). All patients showed some attenuation of the outer nuclear layer of the central retina, which can be a sign of RD but also of macular atrophy in longstanding inflammatory CME (Figure 1). Fluorescein angiography (FA) was done in four patients showing optic disc hyperfluorescence in two of them (Figure 1; patient 5 and 6); and capillary leakage also in two patients (Figure 1; patient 2 and 6). One patient showed a remarkable discrepancy between severe bilateral macular edema on OCT and absence of leakage in the macula on FA. In contrast, another patient showed both severe bilateral macular edema on OCT and severe leakage on FA (Figure 1; patient 1 and 2). In two patients, a full field electroretinogram (ffERG) was performed shortly after the onset of symptoms to rule out a RD. In these cases amplitudes were scotopic and photopic just at or below threshold and latency times were normal in one patient and prolonged in another patient (patient 1 and 5, Table 1). These subnormal ffERG scores were considered to be secondary to uveitis activity as previously has been described.[2]

Based on a combination of clinical characteristics and additional diagnostics uveitis specialists diagnosed IU. The diagnosis was subsequently classified as idiopathic IU following an extensive diagnostic workup by a (pediatric) rheumatologist/immunologist.

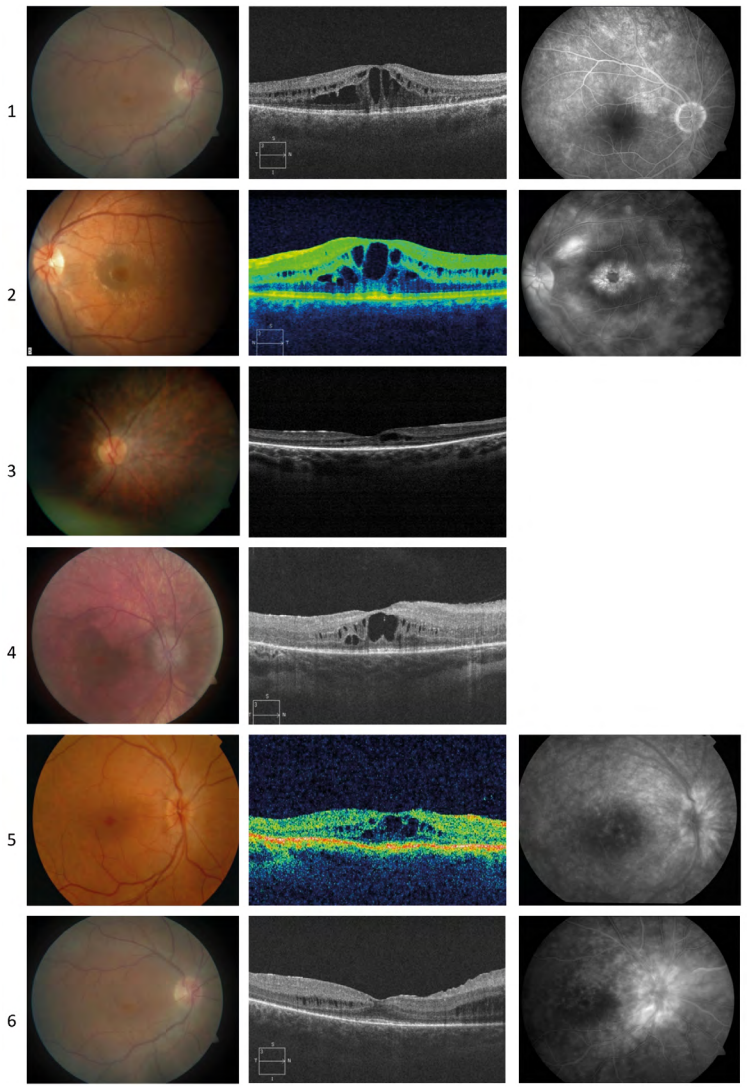

Figure 1. Fundus photographs (left column), optical coherence tomography (middle column), and fluorescein angiography (FA, right column) in six patients with retinal dystrophy; these six patients were initially diagnosed with intermediate uveitis. The patient numbers correspond to the patient numbers shown in Table 1. FA images were not available for patients 3 and 4.

All patients received periocular and/or intraocular corticosteroids with temporarily improvement of CME in 3 patients but CME recurred in 4 to 8 weeks.

Four patients were treated with acetazolamide for at least 3 months but CME did not respond to this treatment. Multiple immunomodulating therapies were initiated in five patients, and biologicals were used in four of them. However, prolonged and combined systemic immunosuppressive therapies failed to reduce CME or inflammation permanently in all patients and did not improve visual acuity.

During follow-up, which ranged from 1 to 8 years, CME of varying degrees persisted and visual acuity deteriorated in all patients (Table 1). Three patients started complaining about nyctalopia. Four patients showed progression of VF defects. Full field electroretinogram recordings were obtained according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Table 1). All patients had severely abnormal scotopic and photopic ffERG responses (Figure 2). In the two patients that had an ffERG shortly after the onset of symptoms, the second ffERG, at 4 and 6 years follow up, showed that responses had deteriorated significantly. The dark adapted threshold proved to be elevated by >2 log in four patients tested. In all patients the results of psychophysical (VF and dark adaptation) testing and ffERG findings led to a diagnosis of RD. Patient genomic DNA was isolated from peripheral blood samples using standard procedures. The DNA was tested for the presence of mutations using Micro-Array Analysis and all sequences were confirmed using DNA sequence analysis confirming the diagnosis RD. Three patients proved to have a mutation in *CRB1 (* one identical novel mutation in two patients with potential pathogenicity), one in *RP1*, one in *USH2A*, and one in two dominant RD genes (Table 1). The last patient had lost contact with her family, so possible dominant inheritance could not be verified. However, in the past, her mother used to complain about nyctalopia.

Here, we report on six young patients with genetically proven RD who initially presented with refractory IU with vitreous inflammation and severe CME. In RD, the vitreous may show cells or debris resembling inflammatory conditions such as uveitis.[3] Macular abnormalities resembling CME and retinal deposits have been described in RD, especially in *CRB1* retinal dystrophy.[4,5] Therefore, in young patients who present with indolent mild intermediate uveitis without pars planitis but accompanied by CME on OCT, an early stage isolated case of RD should be included in the differential diagnosis. In these patients, we recommend direct questioning of nyctalopia and family history for retinal diseases, appropriate VF testing with assessment of the mid and far periphery, measurement of ffERG, and, if necessary, consultation of an ophthalmologist with expertise in the field of retinal dystrophies. An early diagnosis of retinal dystrophy may result in more adequate treatment with avoidance of high dose immunosuppression, which may have significant side effects.

Table 1. Clinical characteristics of six patients with retinal dystrophy who were initially diagnosed with idiopathic intermediate uveitis.

patient	gender	age of onset of symptoms (years)	systemic medication[+]	periocular / intraocular corticosteroid therapy	gene with an identified mutation [x]	visual acuity at presentation (OD/OS)	visual acuity at follow-up (OD/OS) (x) years after onset of symptoms
1	m	12	Acetazolamide Corticosteroid Methotrexate MMF Adalimumab	+	*CRB1* *heterozygous* *p.(Tyr631Cys)*[x] *p.(Cys948Tyr)*	20/32-20/32	20/40-20/50 (7)
2	f	13	Acetazolamide Corticosteroid Methotrexate MMF Adalimumab Infliximab Tocilizumab	+	*CRB1* *heterozygous* *p.(Tyr631Cys)*[x] *p.(Cys948Tyr)*	20/32-20/25	20/63-20/40 (4)
3	f	22	-	+	*PRPF31* *C1792T p.(Arg598Cys)* *SNRNP200* *C910T p.(Arg304Cys)* *heterozygous*	20/40-20/40	20/50-20/50 (7)
4	f	5	Methotrexate	+	*CRB1* *homozygous* *p.(Met1041Thr).*	20/40-20/50	20/63-20/50 (1)
5	m	22	Acetazolamide Corticosteroid Methotrexate MMF Adalimumab Infliximab	+	*USH2A* *heterozygous* *p.(Pro3272Leu) p.(Arg4192Cys)*	20/40-20/32	20/63-20/50 (1)
6	m	16	Acetazolamide Corticosteroid Methotrexate Adalimumab Ciclosporin	+	*RP1* *homozygous* *p.(Pro124fs)*	20/32-20/32	20/200-20/125

[+] MMF = mycophenolate mofetil. [x] This was a novel variant, it is checked in available genetic databases to predict potential pathogenicity and this was the case in the two patients. [*] CME = cystoid macular edema, OCT= optical coherence tomography, central retinal thickness: + = < 400 µm, ++ = 400-500 µm, +++ = >500 µm

	CME on OCT (performed after (x) years)	First visual field (performed after x years)	Electroretinogram (performed after (x) years)	follow-up years before diagnosis retinal dystrophy was made
	+++ (1)	Peritest Some mid-peripheral defects. (1)	scotopic; reduced and delayed photopic; reduced and delayed (7)	7
	+++ (1)	Humphrey 24-2 Some peripheral defects (3)	scotopic; reduced and delayed photopic; reduced and delayed (4)	4
	+ (7)	Goldmann Severe relatively concentric limited (7)	scotopic; absent photopic; reduced and delayed (8)	8
	++ (1)	Goldmann Severe relatively concentric limited (1)	scotopic; absent photopic; only at the highest intensity a very small response (1)	1
	++ (1)	Humphrey 30-2 Severe relatively concentric limited (1)	scotopic; just below the lower limit of normal photopic; just below the lower limit of normal and prolonged latency (7)	7
	+ (1.5)	Humphrey 24-2 Mild peripheral defects (3)	scotopic; absent photopic; reduced and delayed (5)	5

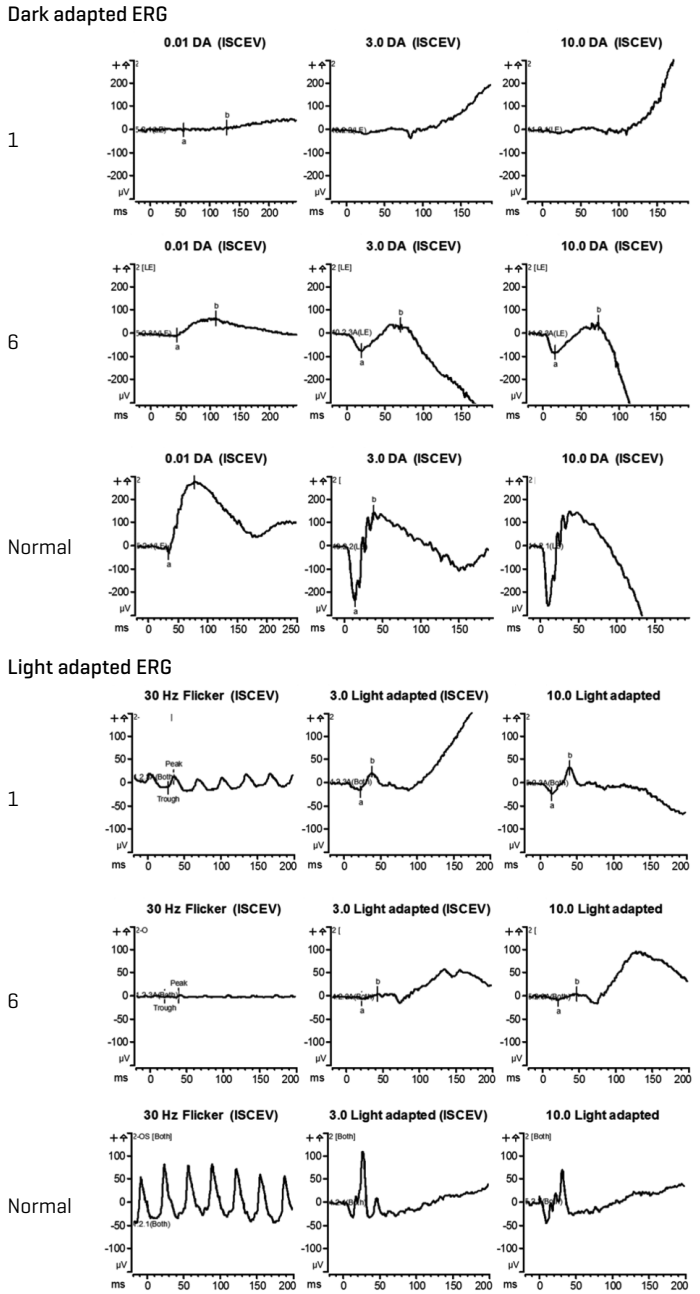

Figure 2. Dark-adapted and light-adapted electroretinograms (ERGs) of Patient 1 and Patient 6, as well as a control ERG ("normal"). DA = dark-adapted. ISCEV = International Society for Clinical Electrophysiology of Vision.

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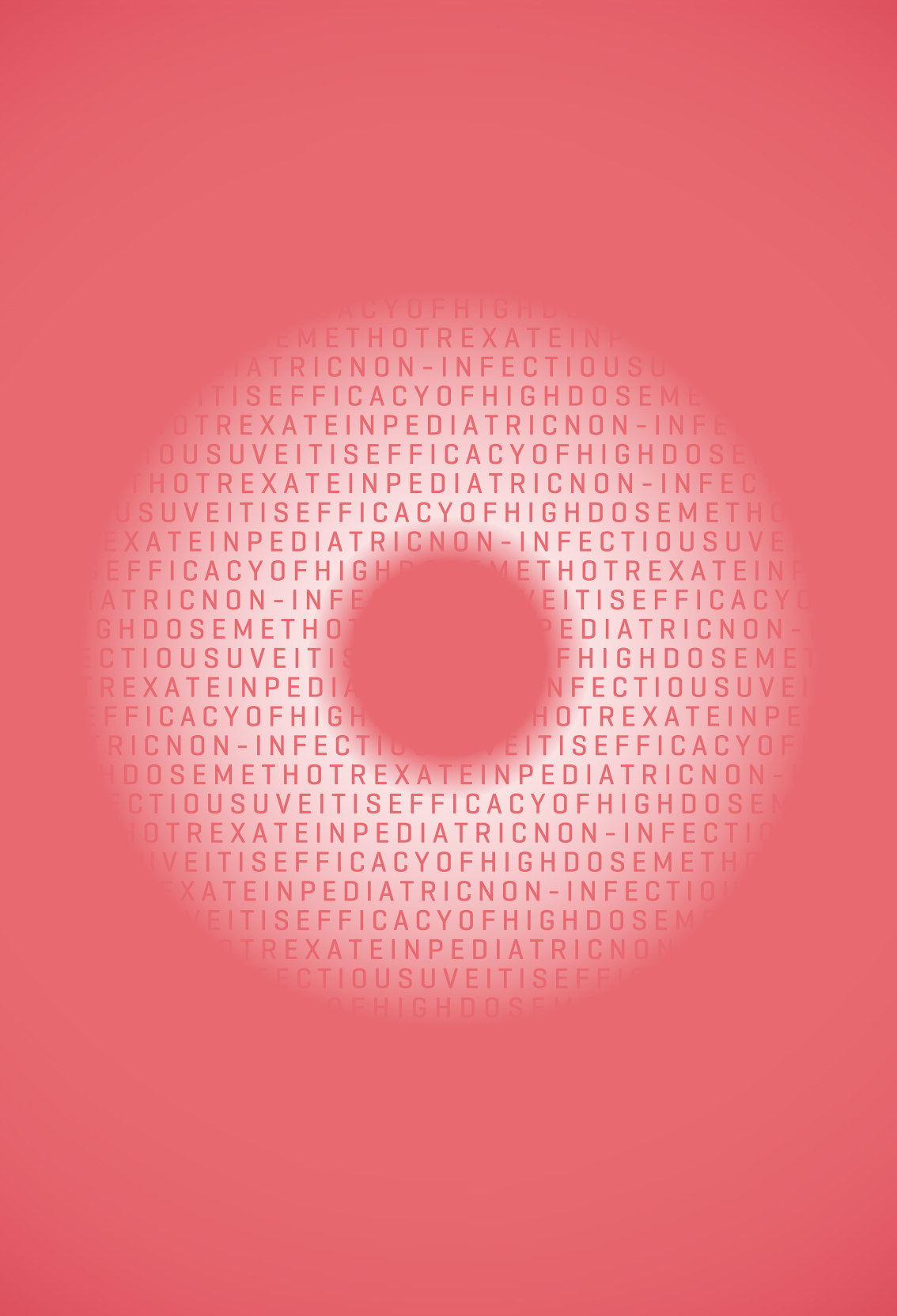

5

EFFICACY OF HIGH DOSE METHOTREXATE IN PEDIATRIC NON-INFECTIOUS UVEITIS

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Ocul Immunol Inflamm. 2018 Oct 22:1-9. [Epub ahead of print]

ABSTRACT

Purpose: To analyze the efficacy of high dose (≥ 15mg/m2/week) methotrexate (MTX) versus low dose (<15mg/m2/week) MTX in relation to time to remission on medication.

Methods: Retrospective observational cohort study of pediatric patients with auto-immune uveitis with or without underlying systemic disease treated with MTX at the University Medical Center Groningen (the Netherlands) between 1990 and 2014. Primary outcome was time to remission on medication, which was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids.

Results: A total of 42 patients were included. Mean age at uveitis diagnosis was 6.5 years (range 1.7 – 14.4), and 22 (52.4%) patients were male. Bilateral disease was found in 33 patients. Most patients (n=25) had anterior uveitis. JIA was the underlying systemic disease in 21 patients. Overall, 28 (66.7%) patients reached remission on medication in (median) 22.5 months (IQR 10.4- 45). Time to remission on medication in the low dose group (median 35.2, IQR 20.5 – 72.1 months) was significantly longer than in the high dose group (median 16.6, IQR 7.8 – 22.5 months) (p= 0.01). No statistically significant differences in ocular complications, steroid-sparing effect, cumulative dosage and side effects of MTX were found between the high and low dose groups.

Conclusion: In this retrospective study on pediatric auto-immune uveitis, high dose MTX was associated with a shorter time to remission on medication as compared to low dose MTX, while side effects were comparable in both groups.

INTRODUCTION

Uveitis is an inflammatory disorder of the eye, involving the uveal tract. It is classified as anterior, intermediate, posterior or panuveitis, depending on the part of the eye affected by the inflammatory process. Uveitis can be associated with a systemic auto-immune disease, can be caused by an infection and it can occur as an isolated ocular condition. In the developed countries, 87 – 89 % of the pediatric uveitis cases are non-infectious and the majority (41.5%) are related to juvenile idiopathic arthritis (JIA)[1].

Pediatric uveitis is a potentially blinding disorder and accounts for 3.2 –15.2% of all cases of legal blindness in the affected eye(s) in the United States[2,3]. Many children with uveitis do not report any symptoms [4]. This may lead to a delay in diagnosis and treatment, resulting in complications such as band keratopathy, posterior synechiae, cataract, glaucoma and amblyopia, which give a guarded prognosis [5]. Early detection and aggressive treatment of uveitis can prevent visual loss and ocular complications [6].

The first line of treatment are local corticosteroids. If these are insufficient, local injections with corticosteroids can be considered. Systemic prednisone is started in case of severe uveitis or in case of failure of the local therapy. In case of chronic uveitis, steroid sparing immunosuppressive therapy may be indicated. Because of its long track record and good safety profile, methotrexate (MTX) is the steroid sparing immunosuppressive agent of first choice in almost all cases of non-infectious pediatric uveitis [7].

MTX is an efficacious drug, since remission on medication is reached in about 70% of pediatric non-infectious uveitis cases [8]. However, MTX also has side-effects such as gastro-intestinal discomfort (nausea and vomiting), which are frequently reported, and the less common hepatic toxicity and bone marrow suppression [9,10]. Also, anticipatory nausea and needle phobia in case of subcutaneous administration of MTX are common.

In pediatric uveitis patients, evidence regarding optimal dosage of MTX is scarce [8,11]. Frequently used medication regimens start with low dose MTX, with increasing doses at 2-6 monthly intervals in case of insufficient effectiveness. In the treatment of JIA there is evidence on the effectiveness of higher starting doses and faster dose-escalation schemes [11-13] . Therefore, it would be relevant to evaluate whether such schemes would also be more efficient in the treatment of pediatric uveitis.

Optimizing the treatment of pediatric uveitis patients would be relevant because vision threatening complications are directly related to uveitis activity [6,14].

Shortening the time to remission on medication will probably reduce or postpone long-term ocular complications and may improve visual prognosis. Also, it seems likely that a higher steroid sparing effect will be achieved with less side effects and complications of systemic corticosteroids. The present retrospective study aims primarily to evaluate the effectiveness of high dose (≥ 15mg/m^2/week) and that of low dose MTX (<15mg/m^2/week) in relation to time to remission on medication. Secondarily, the steroid sparing effect, cumulative dosage of MTX, side effects of MTX treatment, ocular complications and visual acuity are evaluated.

PATIENTS AND METHODS

We performed a retrospective observational cohort study on pediatric patients treated with methotrexate (MTX) for uveitis between 1990 and 2014 at the University Medical Center of Groningen, The Netherlands. This study reflects the daily practice in a tertiary center. The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study. Patients were identified from the digital uveitis database of the University Medical Center of Groningen. All patients who were younger than 18 years of age at the start of their uveitis and who were treated with MTX for longer than 6 months were included. MTX treatment was classified as high (≥ 15mg/m^2/week, maximum of 25mg/week/sc) or low (<15mg/m^2/week) dose, based on the MTX dose given before remission on medication was reached or medication was switched. Based on this classification, patients were divided into a high (≥ 15mg/m2/week) or low (<15mg/m2/week) -dose group. Before 2007, most patients received low dose MTX, and hereafter most patients were treated with high dose MTX. This reflects evolving treatment strategies. Data collection was done from the pediatric and ophthalmological medical records. The diagnosis of uveitis was made by an ophthalmologist specialized in uveitis and dedicated to this patient group. During the follow up period two other ophthalmologists were occasionally involved in the ophthalmological care for these patients. Classification of uveitis was done according to the Standardization of Uveitis Nomenclature (SUN) criteria [15] and was based on the available information in the ophthalmological medical record. Children were evaluated for the presence of an underlying systemic disease by a pediatric rheumatologist. When JIA was diagnosed, it was classified according to the ILAR (International League of the Association for Rheumatology) criteria [16].

General descriptives

For each patient the following descriptives were recorded: age, gender, ethnicity, date of first diagnosis of uveitis (further referred to as: uveitis onset), type of uveitis, laterality, date of onset of arthritis, diagnosis and

subtype of underlying systemic disease, weight and length (at several time points during follow-up), anti-nuclear antibody (ANA) serologic status, HLA B27 status and ophthalmological findings at presentation. Prognostic signs for a worse outcome (young age, male gender, severity of uveitis at presentation, vitreous involvement and oligo arthritis) were recorded [5].

Uveitis diagnosis and classification

Uveitis was diagnosed when cells could be observed in the anterior chamber or in the vitreous. Activity of anterior chamber (AC) inflammation (cells) evaluated by standard slit-lamp examination was recorded according to the recommendations of the SUN working group [15]. Cells in vitreous humor were scored as being present or not. The diagnosis of posterior and panuveitis was made by fundoscopy and in some cases fluorescein angiography (FA) was performed.

Treatment

MTX dosage and route of administration at the start was recorded as mg/m^2/ week/orally or subcutaneously. Indications (uveitis, arthritis or both) and date for MTX dosage changes were documented. The MTX dosage was related to body surface area (BSA) at the moments of dosage change. Body surface area was calculated by the Mosteller formula [BSA (m^2) = (Height(cm) x Weight(kg) / 3600)^{½}] [17]. Measurements of length and weight were performed at the start of the treatment and during follow up. Length and weight values were plotted routinely in the growth curves corrected for age, sex and race. When a value was missing the growth line was plotted between the 2 existing values. Cumulative dosages of MTX were calculated by multiplying the time (weeks) to remission on medication by the dose in mg/m^2 of MTX. Route of administration (oral or subcutaneous) and – in case the route of administration was switched - the indications for switch were noted. Side effects and indications to stop MTX were recorded. Initially, liver enzyme testing is done after four weeks, and thereafter every 3 months. In case of elevated liver enzymes, testing is more frequently performed. The steroid sparing effect of MTX was evaluated by calculating/counting the number of weeks in which patients were treated with oral corticosteroids in a dosage of more than 0.5 mg/kg/day.

In case of cataract or glaucoma surgery (Baerveldt glaucoma implant), patients were given intravenous corticosteroids during surgery followed by a tapering dosage of oral corticosteroids in the period thereafter. In case of glaucoma surgery MTX was stopped for 2 months prior to surgery and re-introduced after the Baerveldt implant was functional. During this period, patients were treated with oral corticosteroids.

Remission on medication

Remission on medication was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids or local steroid injections (subtenon or subconjunctival). During this period local steroid medication such as eye drops or ointment were allowed in a maintenance dosage of less than 4 drops per eye daily. With this treatment regimen, sufficient compliance-adherence was expected and it was regarded as being compatible with daily activities [18]. Patients were advised to use the eye drops during mealtimes and – when necessary- before sleeping. A relapse was defined as a recurrence of the uveitis after a quiet episode described in the patient file. The total follow up time, time to remission on medication, time between dose adjustments and time to cataract and glaucoma surgery were documented.

Visual acuity

The decimal equivalent of the Snellen visual acuity (VA) of the affected eyes was recorded at presentation, six, twelve and twenty-four months and at last follow-up. Snellen VA was converted to logarithm of the minimum angle of resolution units (LogMAR) VA for calculations.

Ocular complications

The following ocular complications were scored per eye; band keratopathy, posterior synechiae, cataract and amblyopia. Ocular hypertension was defined as an intra-ocular pressure above 21 mmHg without treatment [15]. Glaucoma was defined as glaucomatous changes to the optic nerve or visual field [15]. Surgery for medically uncontrollable intra-ocular pressure was separately scored.

Statistics

Statistical analysis was performed by SPSS® software version 22 (SPSS, Inc., Chicago, IL) .A $P < 0.05$ was considered statistically significant. Descriptive statistics were used to present mean and standard deviation (SD) in normally distributed data or median and range if data were abnormally distributed. For the differences between the nominal data in the high and low dose groups we used the Chi-square test. In case of non-normally distributed linked samples, the Wilcoxon test for paired samples and the Mann-Whitney U test for independent samples were used. Analysis of VA at presentation compared to that at six, twelve and twenty-four months and at the end of follow up was done by the independent samples T-test. A Kaplan-Meier survival analysis with a log rank test was used to analyze survival curves and to compare the two treatment groups. Finally, a multiple regression model was used to assess the weight and influence of treatment groups, age, gender, underlying disease and anatomic location of the uveitis on the time to remission on medication.

RESULTS

Patient, ocular and disease characteristics at uveitis onset are summarized in Table 1. A total of 44 (22 male) patients were primarily identified, two of whom (both female, Caucasian JIA- patients with longstanding bilateral anterior uveitis) were excluded because of incomplete data.

Table 1. Patient characteristics

	Total	**low**	**high**	**Difference high/low**
Number of patients	42	25	17	
Mean age at onset uveitis (yrs, SD)	6.5 (± 3.4)	7.6 (± 3.5)	5.0 (± 2.7)	**P 0.01**[¥]
Median follow up (years, range)	5.6 (0.9 – 19.2)	6.9 (1.4 – 15.4)	4.0 (0.9 – 19.2)	**P 0.02**[¥]
Male/female	22/20	13/12	9/8	P 0.95[§]
Anatomic location uveitis				P 0.64[§]
Anterior uveitis	25	15	10	
Intermediate uveitis	7	4	3	
Posterior uveitis	2	2	0	
Pan uveitis	8	4	4	
Bilateral disease	33	20	13	P 0.55[§]
Prognostic poor at presentation*	34	18	16	P 0.11[§]
Ethnicitiy				P 0.53
Caucasian	32/42	19	13	
Other	10/42	6	4	
Underlying systemic disease	21/42	11	10	P 0.35[§]
Cogan's syndrome	1/42	0	1	
JIA	21/42	12	9	P 0.55[§]
Mean age at onset JIA (yrs, SD)	4.1 (± 2.2)	4.4 (± 2.2)	3.5 (± 2.1)	P 0.38[¥]
Systemic	1	1	0	
Oligo articular persistent	10	4	6	
Oligo articular extended	5	4	1	
Poly articular RF-positive	1	1	0	
Poly articular RF-negative	4	2	2	
Lab characteristics				
ANA positive	23/42	15	8	P 0.53[§]
HLA-B27 positive	2/14	0	2	P 0.16[§]

* One or more of the following characteristics present: young age (< 6 years), male gender, severity of uveitis at presentation, signs of vitreous involvement, oligo arthritis. [¥] Mann-Whitney test. [§] Chi-square test. JIA = juvenile idiopathic arthritis, ANA = anti-nuclear antibody

In 4 patients with JIA-uveitis active arthritis (next to the uveitis) was the indication to start MXT. The 17 patients in the high dose group were significantly younger (mean 5.0 ± 2.7 yrs) than the 25 patients in the low dose group (mean 7.6 ± 3.5 yrs, P=0.01) . The follow up time was statistically significantly shorter in the high dose group (median 4.0 yrs, range 0.9 – 19.2) as compared to the low dose group (median 6.9 yrs, range 1.4 – 15.4, P=0.02).

No differences were found between the high and low dose groups regarding severity of the uveitis at presentation and the need for ocular surgery for cataract or medically uncontrollable intra ocular pressure during follow-up (Table 1 and 4).

Table 2. Remission on medication, cumulative MTX dose and steroid use

	Total	Low	High	Difference high/low
Patients (%) reaching remission on medication	28/42 (66.7%)	15/25 (60%)	13/17 (76.5%)	P 0.27§
Time to remission on medication (months, IQR)	Median 22.5 (10.4 – 45.0)	Median 35.2 (20.5 – 72.1)	Median 16.6 (7.8 – 22.5)	**P 0.01***
Median cumulative dose MTX ¶ (mg/m^2, IQR) (n=28)	Median 1329.3 (604 - 2172.3)	Median 1597.4 (693 - 2871.2) (n=15)	Median 1213.1 (538.9 -1934.3) (n=13)	P 0.29*
Patients with remission on oral administration	9/28 (32.1%)	8/9 (88.9%)	1/9 (11.1%)	P 0.06§
Time to remission on oral administration (months, IQR)	Median 20.5 (6.3 – 41) (n=9)	Median 24.4 (n=8) (8.4 – 44.5)	3 (n=1)	P 0.12*
Cumulative dose MTX¶ (mg/m2, IQR) (n=9)	Median 693 (320.3 – 1484.6)	Median 821.2 (396.6 – 1567.7) (n=8)	282.1 (n=1)	P 0.25*
Patients with remission on subcutaneous administration	19/28 (67.9%)	7/19 (36.8%)	12/19 (63.2%)	**P 0.01**§
Time to remission (months, IQR) on sc administration	Median 23.5 (12.5 – 50.4)	Median 62.6 (35.1 – 118.1)	Median 17.2 (8.6 – 23)	**P 0.001***
Cumulative dose MTX¶ (mg/m^2 IQR) (n=19)	Median 1597.3 (956.6 – 2875.5)	Median 2871.2 (1597.3 -9606.1) (n=7)	Median 1276.6 (650.4 -2065.7) (n=12)	**P 0.05***
Steroid use‡ (weeks, IQR) (n=26) ¥	Median 17.2 (11.9 – 26.8)	Median 18.3 (10 – 29.2) (n=13)	Median 16 (11.9 – 22.6) (n=13)	P 0.70*

§ Chi-square test. *Mann-Whitney test. ¶ Total dosage of MTX until remission on medication. ‡ Number of weeks on > 0.5mg/kg daily. ¥ Two patients in the low dose group both with mild JIA related uveitis were not treated with systemic corticosteroids. IQR = inter quartile range. Sc = subcutaneous administration

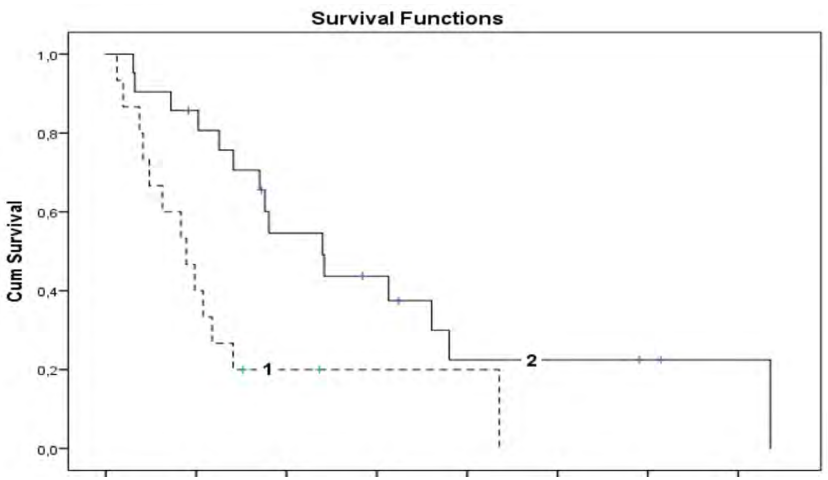

Figure 1. Kaplan-Meier curves showing the time to and chance of remission on medication. Cum = cumulative. 1 = High dose (>15mg/m2/week) methotrexate. 2 = Low dose (<15mg/m2/week) methotrexate. The difference between the groups is statistically significant (P=0.007, Log Rank test). HD= High dose, LD= Low dose

The median starting dose and median maximum dose were both significantly lower in the low dose group. The median starting dose in the low dose group was 10.4 (min 5.7 – max 14.8) mg/m^2/week and in the high dose group 17.9 (min 11.8 – max 24.6) mg/m^2/week (P <0.001). The median maximum dose in the low dose group was 13.4 (min 10.9 – max 14.9) mg/m^2/week and in the high dose group it was 20.7 (min 16.7 – max 25.3) mg/m^2/week (P <0.001). The time to maximum dose of MTX was -although not statistically significant -shorter in the high dose group. The median time to maximum dose in the low dose group was 20.9 (min 2.1 – max 120.1) months versus median 9.1 (min 4.6 –max 21.7, P= 0.10) in the high dose group.

Thirteen patients (76.6%) treated with high dose MTX reached remission on medication after a median of 16.6 months (inter quartile range (IQR); 7.8 – 22.5). In the low dose group 15 (60%) patients reached remission on medication in a median of 35.2 months (IQR; 20.5 – 72.1). The difference in time to remission on medication was statistically significant (P=0.01) (Table 2, Figure 1).

Patients (n=12) treated with high dose subcutaneous MTX had a statistically significantly shorter time to remission on medication (median 17.2 months) than patients (n=7) who reached remission on medication on low dose subcutaneous MTX (median 62.6 months; p = 0.001; Table 2). Of the 9 patients who reached remission on medication on oral MTX, 1 was treated with high dose and 8 with low dose MTX. By using a multivariate linear regression model time to remission on medication was analyzed. Within this model; age, gender, anatomic location of the uveitis, presence of juvenile idiopathic arthritis and the two treatment groups were taken into account. With this model (R^2 = 0.4, P = 0.05, B= 68.6 (CI 24.8 – 112.4)) we found that treatment with a higher dose MTX was associated with a statistically significantly shorter time to remission on medication (P 0.008).

The cumulative dose of MTX, in the 28 patients reaching remission on medication, was lower in the high dose group as compared to the low dose group, but this difference was not statistically significant (Table 2). MTX related side effects were reported by 25 out of 41 patients (Table 3). No statistically significant differences regarding side effects were found between the high and low dose groups.

On average, patients used more than 0.5 mg/kg/day of oral corticosteroids for 17.2 weeks (Table 2); no statistically significant differences in steroid use were seen between the two groups (Table 2). The high dose group had a better visual acuity at presentation (Figure 2), but this difference was not statistically significant. At 6 and 12 months, visual acuity in the high dose group was significantly higher than in the low dose group. At later time points, this difference was no longer statistically significant (Figure 2).

Table 3. MTX-related side effects

	Total n=41*	Low n=24*	High n=17	P value§ High vs Low
Patients	25/41	14/24	11/17	P 0.74
Nausea	13/41	7/24	6/17	P 0.43
Needle phobia	7/41	3/24	4/17	P 0.33
Elevated liver enzymes¶	9/41	5/24	4/17	P 0.78
Combination	4/41	1/24	3/17	P 0.14

*1 missing in the low dose group. § Chi-square test. ¶ Alanine aminotransferase (ALT) above 45 U/L and aspartate aminotrans-ferase (AST) above 40 U/L

Table 4. Ocular complications*

	Eyes	Low dose	High dose	Difference¶ high/low
Band keratopathy	18/75	10/51	8/24	P 0.22
Posterior synechiae	34/75	23/51	11/24	P 0.49
Cataract	38/75	23/51	15/24	P 0.42
Cataract extraction	31/75	23/51	8/24	P 0.56
Baerveldt glaucoma implant	30/75	20/51	10/24	P 0.84
Amblyopia	12/75	7/51	5/24	P 0.26

*Affected eyes at any moment during follow up. ¶ Chi-square test between high and low dose

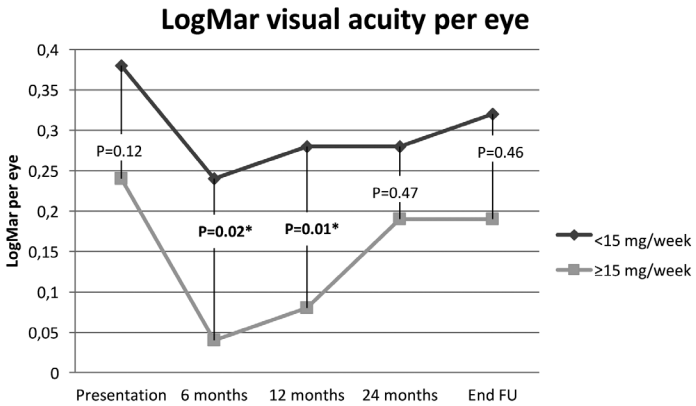

Figure 2. Visual acuity in the high MTX dose group is better at all time points (lower LogMAR visual acuity corresponds to higher Snellen visual acuity) and the difference is statistically significant at 6 and 12 months. FU=follow up,* Independent Samples T-Test

DISCUSSION

This study of 42 pediatric patients with non-infectious uveitis shows that patients who were treated with a high dose of MTX (≥15mg/m^2/week, maximum of 25mg/week/sc) reached remission on medication sooner compared to patients who were treated with a low dose of MTX (<15mg/m^2/week). The data also indicates that an MTX dose of ≥15mg/m^2/week administered by subcutaneous injection is the most effective in establishing rapid remission on medication. With regard to visual acuity measurements at 6 and 12 months the data suggests a favorable outcome in the high dose group. High and low dose groups were comparable with regard to severity of uveitis, incidence of ocular complications and surgery, steroid sparing capacity of MTX, cumulative dose of MTX and side effects.

In our study we found an overall success rate of 67% of MTX in the treatment of uveitis, which is similar to the effectiveness of 70% described in the literature [8]. More patients reached disease remission on subcutaneously administered MTX when compared to oral administration. Time to disease remission on medication did not significantly differ between patients on oral and subcutaneous administration. Patients treated with high dose MTX had a significantly shorter time to remission on medication than the patients treated with low dose MTX. A shorter time to remission on medication may be favorable for the prognosis of an inflammatory disease as was shown for rheumatoid arthritis (RA) in several studies [19-22]. By analogy, it would be plausible to assume that achieving early remission on medication will help to prevent or delay secondary complications of uveitis and to preserve visual function [14,23].

Our retrospective study did not find statistically significant differences in the prevalence of ocular complications at any time point between high and low dose groups, including complications already present at presentation. Therefore and because high dose MTX was mainly given from 2007 onwards, we assume that MTX dose was mainly based on evolving treatment strategies and not primarily on the severity or complications of the uveitis. We did find a statistically significantly better visual acuity in the high dose group at 6 and 12 months, which is suggestive of a better outcome favorable for the daily functioning and development of a child. However, there may be some inclusion bias, since the high dose group had a better, though not statistically significantly better, visual acuity at presentation.

A faster remission reached by a predefined quick dose escalation scheme is probably more rewarding and motivating for a patient than a slow escalation scheme based on dose adjustments because of persisting disease activity. Also, the frequently reported MTX intolerance after longer use of MTX, might be prevented if remission on medication is sooner reached [24,25] . Finally, MTX failure

will be apparent after a shorter time interval when a faster dose escalation scheme is used, thus enabling an earlier switch in therapy. Our high dose group is comparable to the intermediate MTX dose group of Ruperto et al [12] who evaluated the effectiveness and side effects of MTX in JIA. They found a better effect of an intermediate (15 mg/m^2/week) MTX dose as compared to a low MTX dose (10 mg/m^2/week). In addition, they observed that increasing the MTX dose to 30mg/m^2/week (with a maximum of 40mg/week by intra muscular or subcutaneous administration) was not associated with any therapeutic benefit and resulted in more adverse events [12]. In line with that study, our maximum MTX dose is 25 mg/week by subcutaneous administration. Our findings indicating a positive effect of higher MTX dosages in pediatric non-infectious uveitis are in line with the results of a systematic review [8] that showed that the proportion of children responding to MTX is the highest in the studies with an MTX dosage of ≥15mg/m^2/week [26-29].

No significant differences were found in steroid sparing effect, cumulative MTX dosage until remission on medication and side effects of MTX between our two study groups. The first is possibly explained by our reluctance to use systemic steroids in children, since they were mainly given in case of severe uveitis at presentation and peri-operatively. The second reflects that remission on medication is reached sooner in the high dose group as compared to the low dose group. And the latter may be explained by the lower cumulative MTX dosage in the high dose group.

The results of the current study are limited by the fact that the study is retrospective, the numbers of patients are small and there is a large variability in follow up time. The better outcome in the high dose group is possibly influenced by positive developments in treatment options and improved screening programs for JIA uveitis. The reporting of side-effects is influenced in an uncertain way because of the retrospective study design and variability in follow up time. All patients were included from a tertiary center and two patients had to be excluded because of missing data, therefore this study does not represent the total spectrum of pediatric non-infectious uveitis. Also, personal experience or preferences of ophthalmologists and pediatric rheumatologist may have influenced the choice of treatment. The strengths of this study are the systematic way in which data were collected, its adherence to the SUN classification system and guidelines for publications and the dose adjustment for body surface area.

Based on our findings, we would recommend an MTX starting dose of ≥15mg/m2/week with a maximum of 25 mg/week by subcutaneous administration in the treatment of pediatric non-infectious uveitis. After reaching remission on medication a lower (10-15 mg) – possibly oral – maintenance dosage can be considered to maintain remission. Earlier publications about the efficacy of

low dose MTX in rheumatoid arthritis are supporting this [30-33]. Because of the lower and varying bioavailability of oral MTX when compared to subcutaneous administration [34 -36] the effect of switching from subcutaneous to oral administration is difficult to predict. Ayuso et al [29] described a higher relapse rate after withdrawal of MTX in pediatric non-infectious uveitis. Their results indicate that the period of inactivity before withdrawal should be preferably longer than 2 years [29]. They do not describe a dose reduction after remission on medication is reached. By sharing our treatment experiences and advising on steps to optimize treatment regimens, we hope to make a contribution to the improvement of care for children with non-infectious uveitis.

In conclusion, children with non-infectious uveitis can benefit from early treatment with high dose MTX (≥15mg/m^2/week, maximum 25mg/week/sc) preferably by subcutaneous administration. Such a strategy may lead to a shorter time to remission on medication, a higher rate of remission on MTX and similar rates of side effects as in low dose MTX treatment strategies. Future studies, most preferably randomized controlled trials, are needed to confirm these findings.

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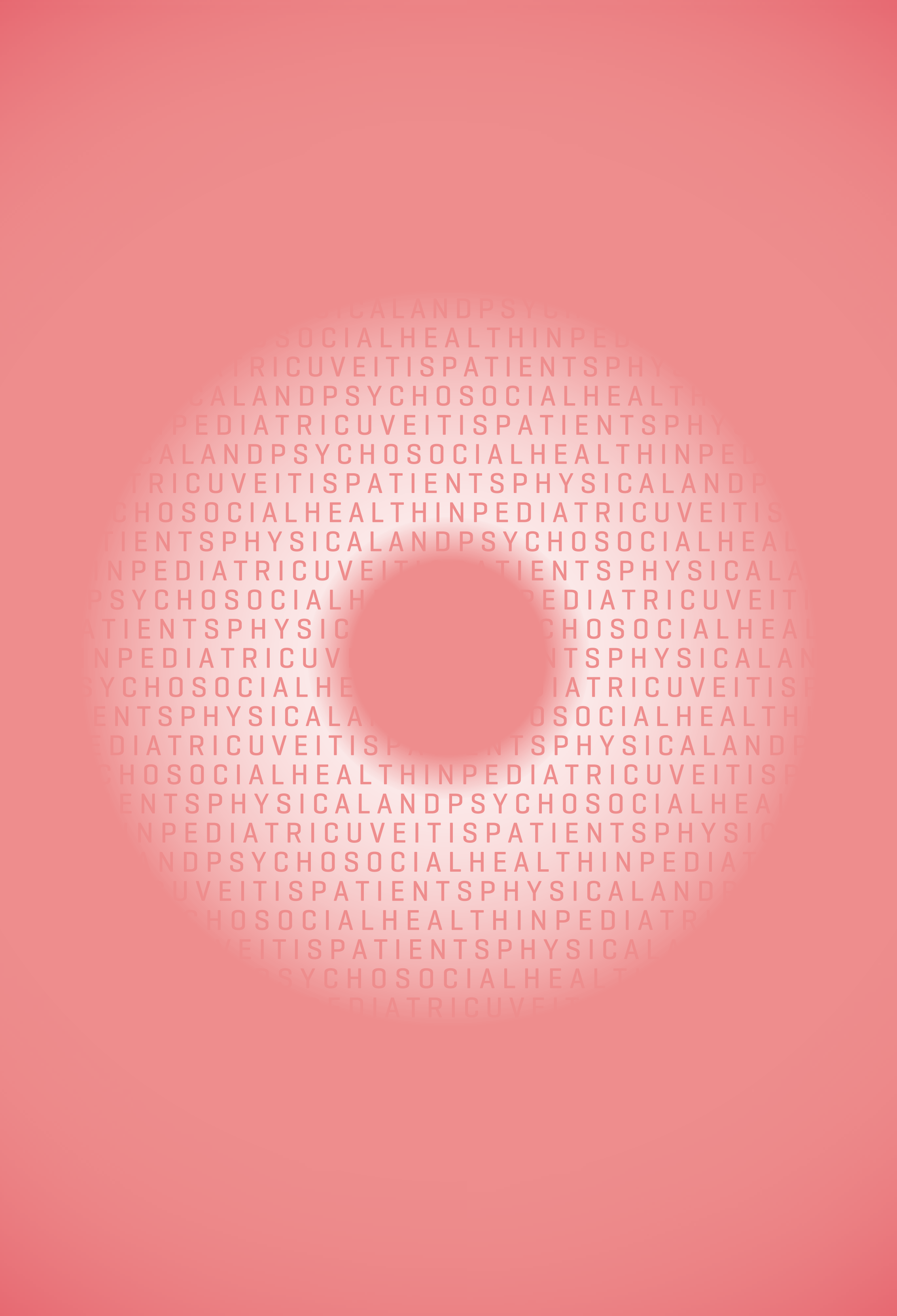
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6

PHYSICAL AND PSYCHOSOCIAL HEALTH IN PEDIATRIC UVEITIS PATIENTS

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Submitted

ABSTRACT

Background: To investigate the possible associations between childhood uveitis and cardio-respiratory fitness, physical activity, health related quality of life and fatigue.

Methods: Cross-sectional analysis of 23 patients with non-infectious uveitis, aged 8-18 years. BMI, exercise capacity, muscle strength and physical activity were measured. Health-related quality of life and fatigue were assessed.

Results: Twenty-three patients were included. Children with uveitis had a higher bodyweight and body mass index when compared to healthy children. Patients with juvenile idiopathic arthritis (JIA) -associated uveitis had a significantly higher BMI than patients with idiopathic uveitis. Children with uveitis had lower cardio-respiratory fitness and they were less physically active when compared to their healthy peers, but they experienced a normal quality of life and normal fatigue. Parents of children with uveitis reported a lower quality of life and more fatigue for their children than parents of healthy children.

Conclusion: Our study indicates that children with non-infectious uveitis are at risk of developing lower physical and psychosocial health. We recommend that investigation and treatment of these aspects should be part of a multidisciplinary treatment approach in children with non-infectious uveitis.

BACKGROUND

Uveitis is an inflammatory disorder of the eye, involving the uveal tract. In the western world the prevalence of pediatric uveitis is 30/100,000 and children account for 5-10% of the total uveitis population [1]. Uveitis may be caused by an infection, may be associated with a systemic auto-immune disease or may occur as an isolated auto-immune reaction without a known underlying cause [2]. In the developed countries, 87 – 89 % of the pediatric uveitis cases are non-infectious and the majority (41.5%) is related to juvenile idiopathic arthritis (JIA)[1, 3].

Patients with auto-immune diseases are more physically inactive compared to the general population [4]. Also, aerobic fitness in children with different types of chronic conditions is reduced and they report more fatigue [5 -7]. In juvenile idiopathic arthritis (JIA), children are also found to be less physically active and have reduced physical fitness levels[8] which does not restore after remission has been reached [9, 10]. The causes of these persistent impairments of physical fitness and physical activity are not known, but it has been suggested that a combination of disease-related factors, treatment (e.g., medication), hypo-activity, and deconditioning could be involved [5, 11, 12].

The pathophysiology of non-infectious uveitis has not exactly been revealed[13]. It is not clear whether the inflammation in this "isolated uveitis" is really limited to the eye or may extend itself systemically [14 – 20]. A number of biomarkers have been identified in JIA-uveitis [20] and in auto-immune uveitis [13]. In oligoarticular and polyarticular rheumatoid factor negative JIA, an elevated erythrocyte sedimentation rate has been confirmed as a predictor of uveitis [21, 22]. Also, in JIA-uveitis a lower level of cytokine IL-29 in aqueous humor (AqH) has been identified as a potential biomarker for uveitis [20]. In children with autoimmune uveitis, an increase in two pro-inflammatory S100 protein subtypes (S100A8/A9 and S100A12) levels in both serum and AqH has been reported [23]. And, in both idiopathic and JIA-uveitis a number of genetic predispositions have been found [13,24].

Systemic treatment in children with idiopathic uveitis who do not respond sufficiently to topical therapy is comparable to that used in JIA. The first line of treatment in pediatric uveitis are local corticosteroids. If local corticosteroids are insufficient, a switch towards steroid sparing immunosuppressive therapy will be made in most cases. Sometimes local injections with corticosteroids can be considered. Systemic prednisone is started in case of severe uveitis and is given peri-operatively in case of intraocular surgery.

Because systemic inflammation can contribute to arteriosclerosis [15 – 17], there is concern that children with inflammatory disease are at higher risk for cardiovascular diseases. In addition to the inflammation itself, systemic

corticosteroids have a negative impact on the cardiovascular risk profile. Well-known side effects are increased bodyweight, hypertension, and accelerated arteriosclerosis [25].

In the literature, information on the physical and psychosocial health of children with uveitis is scarce [26–28]. A recent study on the quality of life (QoL) in children with JIA showed that children with uveitis had poorer vision-related QoL and function when compared to those without uveitis [29]. Some studies on health related (HR) QoL in adult uveitis patients found a decreased HR-QoL compared to the general population[30, 31], whereas one study observed that HR-QoL in adults with JIA-uveitis was not decreased [32]. However, the use of systemic immunomodulatory treatment or the presence of co-morbidity other than uveitis, did negatively influence general HR-QoL scores in adult uveitis patients [32, 33]. Also, in adolescents with non-infectious uveitis despite quiescence of disease and good visual function, certain factors, such as a high number of recurrences, chronicity of the uveitis and fear of blindness were correlated with a decreased HR-QoL [34, 35].

In adults, fatigue has been shown to be a barrier for being physically active [36]. Fatigue is highly present in patients with JIA and is related to many factors including physical activity, physical fitness and HR-QoL of which cause and effect are not exactly known [37]. Also, in our clinical experience, fatigue is often reported by children with uveitis or by their parents. Therefore, uveitis may have a large impact on a child's life and can alter their QoL [26, 27, 34].

To optimize treatment for children with uveitis it is of great importance to get insight in risk factors that have a negative impact on physical and psychosocial health. Regarding the possible negative effects of uveitis, we therefore studied levels of cardio-respiratory fitness, physical activity, muscle strength, health-related quality of life and fatigue in pediatric non-infectious uveitis patients.

PATIENTS AND METHODS

The Medical Ethical Committee of the University Medical Center of Groningen (UMCG) approved the conduction of the study. Patients were included from the departments of children's rheumatology and ophthalmology of the UMCG (the Netherlands) from July till December 2014. Patients aged 8-18 years, known with idiopathic or JIA-associated uveitis were eligible for this study. Patients with infectious uveitis were not included. Patients with co-morbidities, not related to the uveitis, that could influence the outcome of the exercise test, like pulmonary or cardiac diseases, were excluded from the study. All investigations were carried out at one moment following the regular visit. Informed consent was obtained from the parents and from the child if the child was ≥ 12 years old.

Patient characteristics

Information regarding patient characteristics (gender, age), disease characteristics (location of the uveitis, etiology, time since diagnosis, disease status), current treatment (medication, dose, route of administration), complications, and surgery was retrospectively gathered by consulting the medical charts of the patients. Median duration of active disease was recorded. Active disease was defined as observed cells in the anterior chamber or in the vitreous[38]. The diagnosis of posterior and panuveitis was made by fundoscopy and in some cases fluorescein angiography (FA) was performed.

Remission on medication was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids or local steroid injections (subtenon or subconjunctival) [38]. During this period, local steroid medication such as eye drops or ointment were allowed in a maintenance dosage of maximum of 4 times a day.

Patients were examined by an ophthalmologist to determine the activity of the uveitis. The visual acuity was measured with a Snellen chart and was converted to LogMAR-acuity for calculation and statistical purposes [38, 39]. Blindness was defined as a visual acuity less than 0.01 (or LogMAR > 1.3) or a visual field ≤ 10° [40]. Visual impairment was defined as a visual acuity ≥ 0.05 (LogMAR ≤ 1.30) and < 0.3 (LogMAR > 0.50)[40].

Disease activity of JIA was scored on a 0-10 Physician Global Assessment (PGA) scale by a physician. Height and bodyweight were measured and body mass index (BMI = bodyweight(kg)/height^2 (m))was calculated. These measurements were compared with the reference values of Dutch children [41]. Overweight was defined as ≥ 1SD above the mean reference BMI and obesity as >2SD above the mean reference BMI [42].

Physical fitness

Physical fitness was assessed by measuring exercise capacity and muscle strength. Exercise capacity was measured with a cardiopulmonary exercise test using an electronically braked cycle ergometer, and was expressed by peak oxygen consumption (VO_{2peak}) and peak work rate (W_{peak}). We used a ramp version of the Godfrey protocol [43] in which the work rate increased gradually over time with 10, 15 or 20 Watt/min depending on the body height of the patient, as described by Bongers et al [44]. All patients were verbally encouraged to cycle until exhaustion. Maximal exertion was defined as a heart rate of > 180 beats per minute and a respiratory exchange ratio of more than 1.0[44]. The absolute values obtained during the test were compared with the reference values of healthy Dutch children [44]. VO_{2peak} - and W_{peak} per kg bodyweight were calculated and these relative values were also compared with the reference values [44].

General muscle function was assessed by manual muscle testing using the scale of the Medical Research Council (MRC). This scale ranges from 0 till 5, in which 0 means no muscle contraction and 5 means normal muscle power [45]. Isometric muscle strength of four muscle groups was assessed bilaterally by hand-held dynamometry (HHD): the biceps, triceps, iliopsoas, and quadriceps muscles. The assessed values were converted to a total z-score of the four muscle groups and compared with the reference values of healthy children [46].

Physical activity

Physical activity (PA) was subsequently measured by an accelerometer (Actical, Philips respironics). The accelerometer was given on the day of the regular visit and research measurements. The Actical measures accelerations in any plane of movement which are translated into activity counts as a reflection of physical activity. Counts were summed in 1-minute periods. Cut-off points were used to categorize activities as sedentary, light physical activity (LPA), and moderate-to-vigorous physical activity (MVPA)[47]. Patients were instructed to wear the accelerometer during 7 days, for all hours except during sleep and wet-activities (showering, swimming). Patients were also asked to record their physical activities in a diary during the same 7 days as they were wearing the accelerometer. In the diary, patients scored their dominant activity of each 15 minute period of every 24 hours of the day The parents were allowed to help the child with filling out the diary [48]. Patients were asked to register in the diary at which moment they put the accelerometer on and off. Because non-wearing time of the accelerometer can be mistakenly categorized into sedentary activity, we corrected non-wearing time with the information provided in the activity diary. Patients were included in the analysis if they had minimally 4 valid days of wearing the accelerometer. A valid day was defined as a wearing time of minimally 8 hours on a weekday or minimally 6 hours on a weekend day. Mean daily counts were determined by the sum of the total daily counts divided by the number of valid days. The mean amount of time spent in the four different categories of physical activity per day was compared to the values of healthy Canadian youth [49].

Functional ability

Functional ability was assessed by using the Child Health Assessment Questionnaire (CHAQ38). Functional ability was expressed in the disability index (DI) which was calculated as the mean of the maximum scores of all domains. A higher score suggests more disability. The DI of the patients was compared to the DI of healthy Dutch children [50, 51].

Health related quality of life

Health related quality of life (HR-QoL) was evaluated with the Pediatric Quality of Life Inventatory (PedsQL 4.0). The PedsQL measures HR-QoL in four domains:

physical, emotional, social and school functioning[52]. The questionnaire consists of a child self-report and a parent proxy report part and was completed by the child and the parent. A higher score (range 0-100) represents a higher quality of life. The scores of the patients were compared to the scores of healthy children [52, 53].

Fatigue

The level of fatigue in the patients was measured by the PedsQL Multidimensional Fatigue Scale, which measured fatigue in three domains: general fatigue, sleep/rest fatigue and cognitive fatigue [53]. The questionnaire consists of a child self-report and a parent proxy report part and was completed by the child and the parent. A higher score (range 0-100) indicates less fatigue. The scores of the patients were compared to the scores of healthy children [52, 54].

Statistical analysis

Statistical analyses were performed by using SPSS software (version 22). Descriptive statistics were used to present mean and standard deviation (SD) or median and range if data were abnormally distributed. The variables of the children were compared to the reference values of healthy children. Z-scores were calculated for age and gender dependent outcome measures as length, weight, BMI, peak oxygen consumption, peak work rate, and muscle strength. A z-score represents the amount of standard deviations the value differs from the age and gender specific reference value. A z-score above 0 means that the value measured in the study group is higher than in the reference group. A z-score below 0 is the other way around. The one sample t-test was used to compare the normally distributed outcomes of the patients with healthy controls, in case of abnormal distribution of the outcome parameters the one-sample Wilcoxon Signed Rank Test was used. To examine the possible relations between the outcome measurements, we analysed which measurements were correlated to VO_{2peak}, muscle strength, and quality of life. In all analyses a $P < 0.05$ was considered statistically significant.

RESULTS

Forty-two patients were eligible for the study, 24 of whom (57.1%) were willing to participate. One patient was excluded because of pulmonary comorbidities. Thus, 23 patients were included in the study *(Figure 1)*; 10 boys and 13 girls, with a mean age of 12.7 years (range 8.6 – 17.9 years) *(Table 1)*.

Thirteen patients (56.5%) had idiopathic uveitis and the other 10 patients (43.5%) had JIA-associated uveitis. Patients with JIA had no clinically important systemic disease activity at the time of study participation (median PGA 0.0, range 0.0 – 0.5).

At the time of study participation 20 patients (87.0%) were in remission on medication with regard to their uveitis. Three patients, 2 with JIA-uveitis and 1 with idiopathic uveitis, had mild uveitis activity. Eighteen patients (78.6%) used eye drops , 14 (60.9%) used systemic medication , 13 of whom used methotrexate (MTX) *(Table 1)*. Nineteen patients (82.6%) had experienced complications of the uveitis (*Table 2*). Three patients experienced visual loss due to the uveitis, two of whom (8.7%) had unilateral visual impairment and one (4.3%) unilateral blindness. Because of the complications, 9 patients (39.1% of total study population) had undergone surgery; seven of whom (30.4% of total study population) had needed re-surgery *(Table 2)*.

Mean weight and body mass index of the patients were statistically significantly higher when compared to the reference population *(Table 1, Figure 2)*. Nine patients had higher BMI than the reference population, three of whom (13.0%) were obese and six were (26.1%) overweight. Patients with JIA-associated uveitis had a significantly higher BMI z-score than patients with idiopathic uveitis (z-score 1.26 vs 0.22, p=0.02).

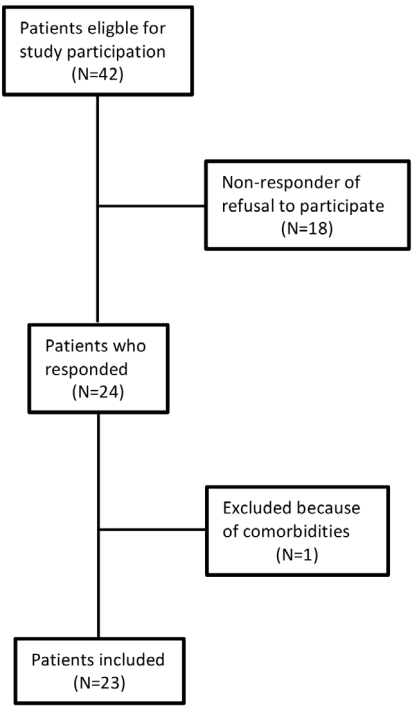

Figure 1. Patient selection

At the cardiopulmonary exercise test, patients reached a mean peak heart rate (HR_{max}) of 191 (±11) beats per minute. At maximal exertion, four patients did not reach a heart rate of > 180 beats per minute, but all patients reached a respiratory exchange ratio of more than 1.0, meaning that the exercise is intense because carbon dioxide (CO_2) production by the working muscles becomes greater and more of the inhaled oxygen (O_2)gets used rather than being expelled. Median VO_{2peak} was comparable to VO_{2peak} of healthy children. Mean VO_{2peak} per kilogram bodyweight, median W_{peak}, and mean W_{peak} per kilogram bodyweight were all significantly lower than the reference value of healthy children (p<.05) *(Table 1, Figure 2)*.

All patients had a normal general muscle power (MRC-scale 5). However, in comparison to healthy controls maximal isometric muscle strength was

significantly reduced in patients ($p < .01$)(*Figure 2*). There was no difference in physical fitness (VO_{2peak}, W_{peak}, and muscle strength) between patients with JIA-associated uveitis and patients with idiopathic uveitis.

Measurement of physical activity by the accelerometer was valid in 21 children (91.3%). Patients were physically active during 182 (light) and 36 minutes (moderate-to-vigorously) per day, respectively. This is significantly lower than in healthy Canadian children ($p < 0.001$) *(Table 1)*[30]. There was no difference in the amount of moderate-to-vigorous physical activity (MVPA) between patients with JIA-associated uveitis and patients with idiopathic uveitis.

Patients reported a normal functional ability *(Table 1)* and a normal HR-QoL. In contrast, parents indicated that their children had a lower quality of life compared to a reference group of parents of healthy children *(Table 1)*. The same was seen with fatigue. Children with uveitis did not experience more fatigue than healthy children, but their parents judged their children were more fatigued compared to parents of healthy children. There was no correlation between patient reported and parent reported fatigue and between physical activity and fatigue scores. Patient and parent scores on HR-QoL and fatigue did not differ between patients with JIA-associated and idiopathic uveitis.

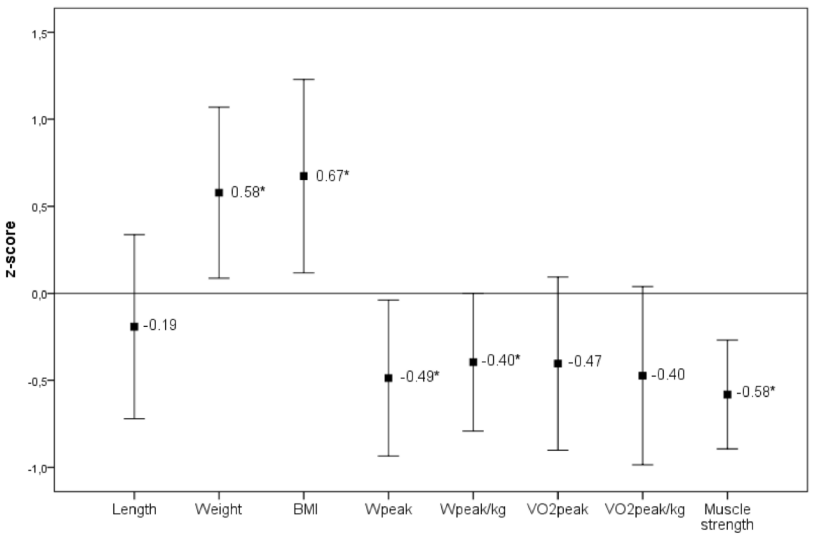

Figure 2. Z-scores. The z-score represents the amount of standard deviations the value differs from the age and gender specific reference value. Values are presented as mean with 95% confidence interval. Weight = weight for age, BMI = body mass index, VO2peak = oxygen consumption at peak exercise, VO2peak/kg = oxygen consumption per kg bodyweight, Wpeak = peak work rate, Wpeak/kg = peak work rate per kg bodyweight, Muscle strength = the sum of biceps, triceps, iliopsoas, and quadriceps muscles divided by eight as measured by hand-held dynamometry. * Significant at $p < 0.05$ (see Table 1)

Table 1. Patient characteristics and outcome measurements compared to reference values

	Number (%)	Mean (±SD) / Median (range)	Reference value	Z-score	Sig.
Age (yrs)		12.7 (± 2.7)			
Male	10 (43.5%)				
Female	13 (56.5%)				
Anthropometrics					
Length (cm)		156.7 (± 17.5)	*AGD*[23]	-0.19	p = 0.46
Weight (kg)		50.3 (± 17.7)	*AGD*[23]	0.58	**p = 0.02**
BMI		19.9 (± 4.0)	*AGD*[23]	0.67	**p = 0.02**
Underlying systemic disease					
juvenile idiopathic arthritis (JIA)	10				
PGA JIA activity	0				
Uveitis[a]					
Idiopathic	13 (56.5%)				
JIA associated	10 (43.5%)				
Time since diagnosis (yrs)		5.88 (1.28 – 12.71)			
Remission duration (yrs)[b]		2.09 (0.17 – 8.35)			
Duration of active disease (yrs)		3.19 (0.55 – 11.91)			
Active disease (uveitis)	3 (13%)				
Treatment[c]					
Local medication	18 (78.3%)				
Steroids	17 (73.9%)				
Anti-glaucoma	10 (43.5%)				
Mydriatics	1(4.3%)				
Systemic medication	14 (60.9%)				
Steroids	1 (4.3%)				
MTX	13 (56.5%)				
Biological	7 (30.4%)				
Physical fitness					
VO_{2peak} (l/min)		2.1 (± 0.84)	*AGD*[44]	-0.40	p = 0.11
VO_{2peak}/kg (l/min/kg)		41.3 (± 8.1)	*AGD*[44]	-0.47	p = 0.07
W_{peak} (Watt)		163 (± 65.5)	*AGD*[44]	-0.49	**p = 0.04**
W_{peak}/kg (Watt/kg)		3.3 (± 0.6)	*AGD*[44]	-0.40	**p = 0.05**
HDD (Newton)		200.3 (± 68.2)	*AGD*[46]	-0.58	**p = 0.001**
Questionnaires					
Functional ability		0.22 (0 – 1.44)	0.20[51]		p = 0.15
HR-QoL Child		84.2 (± 10.0)	83.91[50,51]		p = 0.76
HR-QoL Parent		77.0 (± 11.7)	82.29		**p = 0.04**
Fatigue Child		82.9 (± 12.1)	80.49[54]		p = 0.25
Fatigue Parent		72.0 (± 18.0)	89.63		**p < 0.001**
Physical activity (N=21)[d]					
Light physical activity (min)		182 (± 75)	256[49]		**p < 0.001**
MVPA (min)		36 (± 16)	54[49]		**p < 0.001**

SD = standard deviation, *AGD* = age and gender dependent, yrs = years, min= minutes, BMI = body mass index, PGA = physician global assessment VO_{2peak} = oxygen consumption at peak exercise, VO_{2peak}/kg = peak oxygen consumption per kg bodyweight, W_{peak} = peak work rate, W_{peak}/kg = peak work rate per kg bodyweight, HHD = hand held dynamometry, MVPA = moderate-to-vigorous physical activity, HR-QoL = health related quality of life. [a] See Table 2 for further specifications. [b] Remission on medication. [c] Because some patients had more than one medication, the cumulative percentages can be different from the total percentages. [d] In 2 patients the measurement of physical activity was invalid.

Table 2. Ocular features

	Number of Patients (N=23)	Percentage	Median	Range
Uveitis localization				
Anterior	15	65.2 %		
Intermediate	4	17.4 %		
Posterior	0	–		
Panuveitis	4	17.4 %		
Bilateral disease	16	69.6%		
Visual acuity (LogMAR*)				
Worse eye			0.05	-0.08 – 2.48
Better eye			0.00	-0.08 – 0.22
Unilateral impairment**	2	8.7%		
Unilateral blindness**	1	4.3%		
Complications**	19	82.6%		
Cataract	13	56.5%		
Glaucoma	13	56.5%		
Posterior synechiae	10	43.5%		
Band keratopathy	5	21.7%		
Amblyopia	1	4.3%		
Surgery***	9	39.1%		
Cataract extraction	8	34.8%		
Baerveldt-implantation (anti-glaucoma treatment)	8	34.8%		
Re-surgery	7	30.4%		

LogMAR= Logarithm of the Minimum Angle of Resolution. * A lower LogMAR visual acuity score corresponds to higher Snellen visual acuity and vice versa. ** Visual impairment was defined as a visual acuity ≥ 0.05 (LogMAR ≤ 1.30) and < 0.3 (LogMAR > 0.50), blindness was defined as a visual acuity less than 0.01 (or LogMAR > 1.3) or a visual field ≤ 10° [40]. *** Because some patients had more than one complication, surgery or medication, the cumulative percentages can be different from the total percentages.

Table 3. Correlations

	VO_2peak*		HDD*		HR-QoL child		HR-QoL parent	
	P	p	r	p	r	p	r	p
Gender	-0.15	0.51	-0.13	0.55	-0.25	0.25	-0.06	0.79
Age	0.37	0.09	0.51	**0.01**	0.40	0.06	0.30	0.17
Duration of active disease	-0.28	0.19	-0.12	0.59	-0.16	0.47	-0.63	**0.001**
systemic medication	-0.28	0.20	-0.05	0.81	-0.07	0.75	-0.21	0.33
BMI*	0.30	0.17	0.69	**< 0.001**	0.38	0.08	-0.11	0.63
HDD*	0.53	**0.01**			0.55	**0.01**	0.19	0.38
VO2peak*			0.53	**0.01**	0.35	0.10	0.26	0.24
MVPA	0.05	0.85	-0.08	0.74	0.04	0.86	0.24	0.32
DI					-0.64	**0.001**	-0.10	0.64
HR-QoL child	0.35	0.10					0.06	0.78
HR-QoL parent	0.26	0.24			0.06	0.78		
Fatigue child	0.36	0.09	0.46	**0.03**	0.83	**< 0.001**	-0.21	0.34
Fatigue parent	0.33	0.12	0.21	0.33	-0.04	0.85	0.73	**< 0.001**

Values presented as Spearman correlation (P) or Pearson correlation (r) and statistical significance (p). * Z-scores. Abbreviations: BMI = body mass index, HDD = hand-held dynamometry measurements for muscle strength, VO_2peak= peak oxygen consumption (l/min), Wpeak = peak work rate (Watt), MVPA = moderate-to-vigorous physical activity, DI = disability index, HR-QoL = health related quality of life.

Correlations are shown in Table 3.The correlation-coefficient between VO_{2peak} and W_{peak} was 0.94 (P = < 0.001), VO_2peak was therefore used and interpreted as a measure for exercise capacity. Muscle strength (HDD) was correlated with higher VO_2peak. Older age and higher BMI were correlated with higher muscle strength. Higher child reported HR-QoL was correlated with higher muscle strength and less fatigue (higher score means less fatigue). Higher disability was correlated with lower HR-QoL. Longer duration of active disease was correlated with lower HR-QoL reported by the parents about their child. Less fatigue was associated with a higher HR-QoL reported by the parents about their children.

DISCUSSION

Patients with uveitis have higher BMI compared to healthy children, they are at risk for reduced physical fitness levels as indicated by a lower aerobic exercise capacity and reduced muscle strength when compared to the healthy pediatric population. Also, children with uveitis are less physically active (PA), and their parents report a lower quality of life (HR-QoL) and more fatigue for their children when compared to parents of healthy children. In contrast, the children themselves report a normal HR-QoL and fatigue. The children with JIA-uveitis have a statistically significantly higher BMI than the children with idiopathic uveitis. No differences are found between JIA and idiopathic uveitis patients in physical fitness levels.

We found a significantly higher percentage of overweight (26%) and obese (14%) patients compared to the Dutch population, 13-15% and 2.2%, respectively. In patients with JIA-uveitis BMI was significantly higher compared to non JIA uveitis. Corticosteroids are a well-known cause of weight gain[12], however in our study only one patient used low dose (5 mg) systemic corticosteroids and most of the patients had not used systemic steroids for a long period of time. In JIA, contradictory results concerning obesity have been found and the cause has not been revealed yet [55, 56]. A possible explanation is a more sedentary lifestyle which we also found in this study. There are indications that obesity in JIA can result in higher inflammatory markers and an increased risk of atherosclerosis[11, 12, 57]. It is reasonable to assume that this risk is comparable in patients with uveitis, so healthcare professionals and carers should be aware of weight gain in patients with uveitis.

Children with uveitis have lower aerobic exercise capacity levels than their healthy peers, but relatively well preserved levels when compared to children with other chronic conditions [5, 6]. Interestingly, we found no differences in aerobic exercise capacity between JIA and idiopathic uveitis patients. The arthritis of the ten patients with JIA uveitis was in remission. It is known that the aerobic exercise capacity in patients with JIA does not restore after remission has been

reached[9]. We assume that comparable underlying mechanisms could play a causative role in uveitis but their nature has not yet been revealed . The general assumption is that reduced levels of aerobic fitness are caused by a combination of disease-related pathophysiology, treatment (e.g., medication), hypo-activity, and deconditioning[5, 11, 12].

Patients with uveitis have decreased muscle strength that is possibly caused by the same combination of mechanisms that are responsible for the reduced exercise capacity. From the literature it is known that low exercise capacity, decreased muscle strength, the inflammation itself, circulating cytokines and the use of systemic corticosteroids are correlated with an increased risk of cardiovascular diseases[11, 12, 58, 59]. In children with uveitis, these factors are present. Therefore, physicians should be alert and try to eliminate extra cardiovascular risk factors.

Our patients report 32 minutes of moderate-to-vigorous physical activity (MVPA) per day which is considerably less than the 60 minutes of daily MVPA as recommended by the WHO and the MVPA of the reference group[49, 60]. Similar results have been found for adolescents with JIA[8, 9]. Hypoactive children are often at greater risk of preventable health problems, such as obesity and cardio-metabolic diseases [5 , 57]. Cardiovascular health in children can be improved by sufficient physical activity (PA) and physical fitness [61], whereas PA also has a beneficial effect on HR-QoL[4]. In several auto-immune diseases, PA has been shown to be safe, to improve HR-QoL and to reduce fatigue [4].

The parents of our patients score a lower quality of life and higher levels of fatigue for their children than parents of healthy children, whereas the children themselves report outcomes comparable to those of their healthy peers on both questionnaires. This difference is probably due the proxy-problem, a known variation in patient and parent-report [62]. In the measurement of quality of life, parents tend to score a lower quality of life for their chronically ill children than the children themselves. This is possibly due to the differences in adaptation to a chronic disease in child and parent. Parents are possibly more aware of the health risks and have a broader perspective than children [62, 63]. Also, it is likely that the parent- reported HR-QoL and fatigue are influenced by their frequent visits to the hospital and their efforts associated with the medical treatment of their child.

The positive correlations in our study between exercise capacity, muscle strength and BMI are not supported in the literature [65]. Also, the reported loss of HR-QoL [52, 66] and increase in fatigue in children with overweight is not found in our results. We cannot explain these findings. Perhaps the significantly lower PA combined with adaptation in coping strategies by the children are responsible for these contradictory results. We did not investigate body composition, so we

cannot comment on the influence of differences between muscle and fat mass on measured BMI in relation the muscle strength and exercise capacity. The negative correlations between lower HR-QoL (reported by children) and loss of functional ability and between lower HR-QoL (reported by parents) and longer disease duration are in line with the literature [33, 51 – 54, 67].

Limitations of the study

We performed this study as a pilot with a small number of patients. Furthermore, this study is cross sectional and most patients were in disease remission. Patients in other phases of the disease may have different results. Also, there is an unknown selection bias, because not all eligible patients participated. Another possible bias is that this study was conducted in a tertiary center. In the Netherlands, children with uveitis who require systemic therapy are treated and managed in tertiary (in most cases university) centers. The results thus do not represent the total spectrum of pediatric non-infectious uveitis and the results and conclusions should be interpreted in this way.

Clinical implications

We recommend that clinicians discuss the importance of sufficient levels of physical fitness and PA during outpatient visits with patients and their parents. Also, close monitoring of body weight should be performed and the prevention of overweight should be a treatment goal.

CONCLUSION

This pilot-study investigated the physical and psychosocial consequences of uveitis in childhood. We showed that patients with non-infectious uveitis are at risk of developing cardiovascular risk factors early in life. Children with uveitis have a higher BMI, lower cardio-respiratory fitness and are less physically active when compared to healthy peers. Furthermore, their parents report a lower quality of life and more fatigue for their children compared to the parents of healthy children. It remains undecided whether this can be attributed to the systemic treatment or the inflammatory disease, since children with idiopathic non-infectious uveitis had similar test results as children with JIA-uveitis. Clinicians should discuss the importance of sufficient levels of physical fitness and PA with patients and their parents during outpatient visits. With the current knowledge and the results of our study we believe we can contribute to the optimisation of the treatment for children with uveitis. Treatment of paediatric uveitis should be aimed at improving the physical and psychosocial health and reducing cardiovascular risk factors in this vulnerable group of patients in addition to maintaining and preserving vision.

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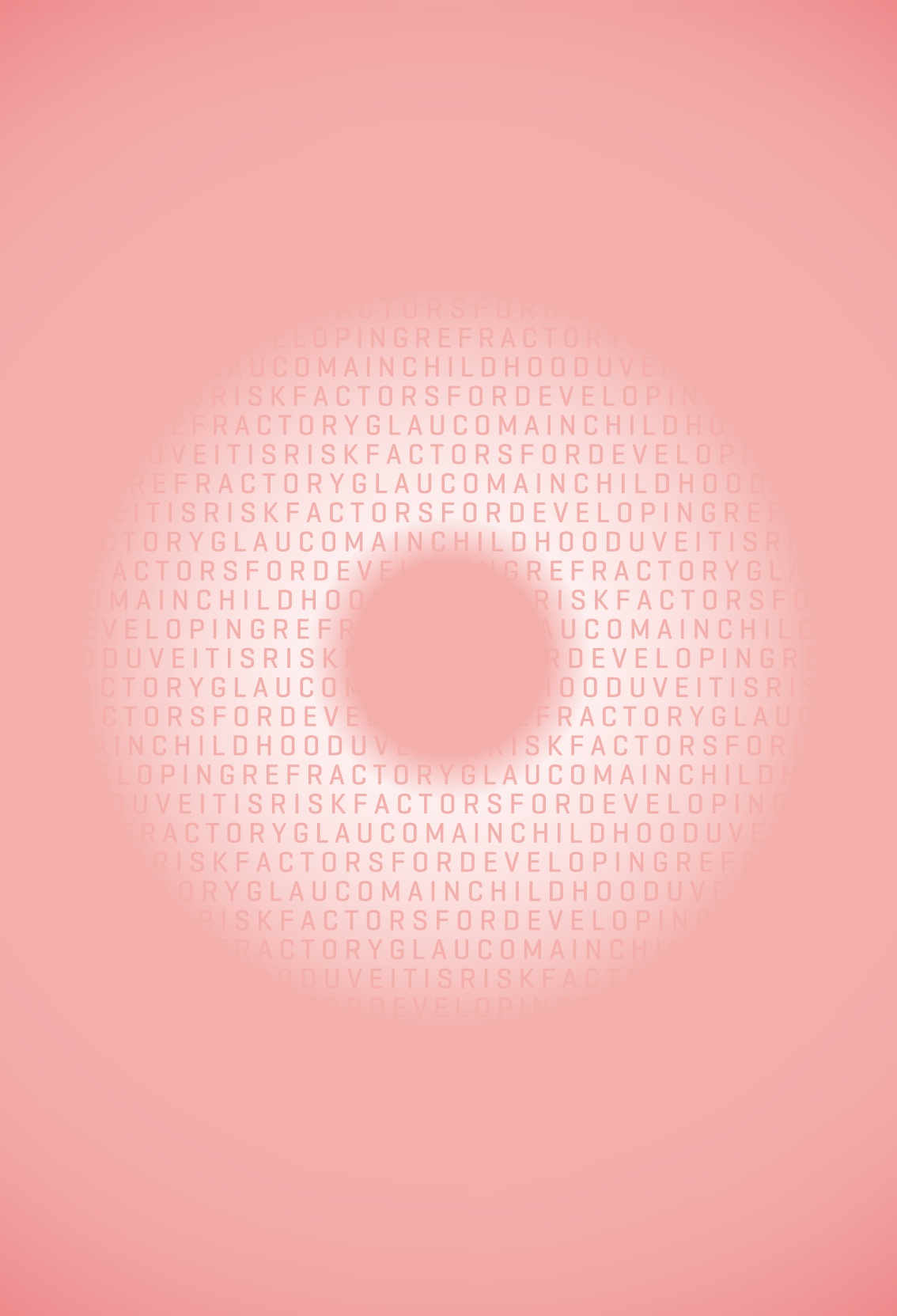

7

RISK FACTORS FOR GLAUCOMA SURGERY IN CHILDHOOD UVEITIS

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To be submitted

ABSTRACT

Purpose: To identify risk factors for medically uncontrollable high intraocular pressure (IOP) secondary to uveitis in children.

Methods: Patients diagnosed with uveitis before their 18th birthday and with a minimal follow-up of one year were included from the ophthalmology departments of the University Medical Center Groningen and the University Medical Center Utrecht in a retrospective case-control study.

Results: A total of 196 patients were included, 85 of whom had undergone glaucoma surgery (cases). Compared to those without glaucoma surgery (controls), cases were younger (median age 6 versus 8 years, P=0.008), uveitis was more often located anteriorly (78% versus 62%, P=0.02) and was predominantly associated with juvenile idiopathic arthritis (JIA) (62% versus 35%, P<0.001). During follow-up, cases underwent cataract surgery more often (80% versus 31%, P<0.001), had higher maximum IOPs (median IOP 37 mmHg versus 27 mmHg, P<0.001), and more often used > 2 types of glaucoma medication (83% versus 24%, P<0.001). Of those needing > 2 types of glaucoma medication 68% underwent glaucoma surgery within one year. Gender, bilaterality, visual acuity and ocular complications at diagnosis, ANA positivity, use of systemic immune-suppression, and cataract surgery before glaucoma surgery were not significantly different between the two groups. Cox survival analysis showed that anterior uveitis (P = 0.04) and increased IOP at presentation (P = 0.02) were predictive of increased risk of needing glaucoma surgery.

Conclusion: Anterior location of the uveitis and higher IOP at presentation are associated with an increased risk of glaucoma surgery. Patients who need > 2 types of glaucoma medication are likely to need glaucoma surgery, usually within 1 year after increasing the number of medications.

INTRODUCTION

The most common causes of vision loss in childhood uveitis are cataract, band keratopathy, glaucoma and cystoid macular edema[1,2]. The reported prevalence of secondary glaucoma in children with uveitis ranges between 5 – 25 %[1–4] and IOP elevation in childhood uveitis has been reported to range between 3–51%[3].

Secondary glaucoma occurs when uveitis is associated with elevated intraocular pressure (IOP) and optic nerve damage, resulting in irreversible visual field loss. Damage of the trabecular system due to inflammation, but also the topical steroids used as treatment of uveitis can increase the IOP. Secondary glaucoma in childhood uveitis has an unpredictable course, with large IOP fluctuations, varying responses to eye-pressure lowering medication, and a frequent steroid-response[5]. Increased IOP is initially treated pharmacologically in a stepladder approach. If after these pharmacological steps IOP is still unacceptably high, glaucoma surgery is required. To obtain the best long-term visual outcome, it is important to identify the children who are at increased risk for the development of secondary glaucoma at an early stage and to treat them by glaucoma surgery before irreversible damage has occurred[6].

Two previous studies on risk factors for secondary glaucoma reported a female preponderance, juvenile idiopathic arthritis (JIA) as the most common etiology, and anterior uveitis as predictive anatomical site for developing ocular hypertension or glaucoma in children with uveitis[7,8]. Heinz et al show a significantly higher need for glaucoma surgery in childhood uveitis compared to uveitis in adults[8]. A study to identify risk factors for the need of glaucoma surgery in medically uncontrollable raised IOP secondary to childhood uveitis has not yet been performed.

The aim of this study is to identify risk factors of raised IOP needing glaucoma surgery in childhood uveitis. For this purpose, we evaluated a large group of children with uveitis and compared those who needed surgery to those who did not. Identification of such factors may contribute to the early detection of the need for glaucoma surgery in this patient group, thus enabling surgery at an early stage of the disease and the prevention of irreversible damage.

PATIENTS AND METHODS

Patients diagnosed with uveitis before their 18th birthday and with a minimal follow-up of 1 year were included from the departments of ophthalmology of the University Medical Centers of Groningen (UMCG, the Netherlands) and Utrecht (UMCU, the Netherlands). Patients were diagnosed with uveitis between 1989 and

2016 and were identified from the uveitis databases of both centers. The Medical Ethical Committee of the UMCG and UMCU approved the conduction of the study. All the patients needing glaucoma surgery ("cases") from both centers were included. The control group ("controls") consisted of all patients without glaucoma surgery from the UMCG, whereas for the UMCU cohort one random patient not needing glaucoma surgery was used as a control for each patient needing glaucoma surgery. Data collection was done from the ophthalmological medical records.

Uveitis diagnosis

The diagnosis of uveitis was made by ophthalmologists specialized in childhood uveitis. Classification of uveitis was done according to the Standardization of Uveitis Nomenclature (SUN) criteria[9] and was based on the available information in the ophthalmological medical records. Children were evaluated for the presence of an underlying systemic disease by pediatric rheumatologists. Activity of anterior chamber (AC) inflammation (cells) evaluated by standard slit-lamp examination was recorded according to the recommendations of the SUN working group[9]. Cells in the vitreous were scored as being present or not. The diagnosis of posterior and panuveitis was made by fundoscopy and on indication fluorescein angiography (FA) was performed.

Glaucoma diagnosis

The assessment of necessity for glaucoma surgery was done by ophthalmologists specialized in glaucoma and was based on a combination of intraocular pressure level, the number of different types of glaucoma medication, and IOP-related irreversible changes to visual field or optic nerve.

We analyzed the data of one eye per patient. In the surgery group, if both eyes underwent glaucoma surgery, the eye that first underwent surgery was used. In the control group, if the uveitis was bilateral, the eye with the first presentation of uveitis was used. If both eyes were affected at the same time, the worst eye with regards to visual acuity, complications and IOP at diagnosis was chosen. When both eyes were equally affected a random eye was chosen.

General descriptives

The following information was recorded: age at onset of uveitis, gender, classification of uveitis, anti-nuclear antibodies (ANA) status, ocular complications at presentation, surgical procedures and systemic medication. Intra-ocular pressure and anti-glaucoma medication were recorded at regular intervals during follow-up until glaucoma surgery or in the control group until the last ophthalmic examination. IOP at disease remission was measured when observable inactive disease for longer than 3 months was documented, with a maximum daily maintenance dosage of local steroids of 3 times per day, with or without systemic immunosuppressive medication.

Ocular complications

Complications were scored as anterior when band keratopathy, cataract, or posterior synechiae were present. Posterior complications were scored when macular edema or papillitis were present. All patients needing cataract surgery during follow up were recorded. Additionally, as possible risk factor for glaucoma surgery, cataract surgery > 3 months prior to glaucoma surgery was recorded.

Visual acuity

The decimal equivalent of the Snellen visual acuity (VA) of the affected eyes was recorded at presentation. The Snellen VA was converted to logarithm of the minimum angle of resolution units (LogMAR) VA for calculations.

Data analysis

Data were statistically analyzed with SPSS 23.0.0 (SPSS Inc, Chicago, Illinois, USA). A $P<0.05$ was considered statistically significant. Bonferroni correction was applied where needed. Descriptive statistics were used to present mean and standard deviation (SD) in normally distributed data or median and inter quartile range (IQR) in non-normally distributed data. In case of non-normally distributed linked samples, the Wilcoxon test for paired samples and the Mann-Whitney U test for independent samples were used. For the differences between the nominal data groups we used the Chi-square test. A Cox survival analysis was performed. All categorical variables were dichotomized for the purpose of this analysis. The need for glaucoma surgery was defined as the event. Covariates present at baseline with $P\leq0.2$ were analyzed as predictors in a backward stepwise conditional method. To correct for differences in data between the two centers, we added the center as a covariate to the multivariable model. The survival curve was graphically displayed as mean value for all covariates. In one covariate, 20% of the data-points were missing. Missing data patterns were analyzed and the data was classified as missing at random (MAR) based upon Little's MCAR test (supplementary data: Table 2). Missing data was compensated for by imputing mean values (supplementary data: Table 2). Next to that, analyses were repeated with missing data compensated by multiple imputation and outcomes were compared to original data and data with imputed values (supplementary data: Table 2, 3)[10,11].

RESULTS

Patients characteristics are summarized in Table 1. In total 196 patients (85 female) were included in the study. In the univariable comparisons, cases were younger than the controls (median age 6 versus 8 years, $P=0.008$).

Table 1. Characteristics complete cohort

	Total (n=196)	Glaucoma surgery (cases, n=85)	No glaucoma surgery (controls, n=111)	P-value
Number of patients	196	85	111	
Median age at uveitis onset (yrs), (IQR)[b]	7 (4-10)	6 (4-9)	8 (5-11)	**0.008**[a]
Center 1[c]	97 (49%)	34	63	
Center 2[d]	99 (51%)	51	48	
Gender – female	85 (43%)	53	32	0.51[e]
Bilateral disease	134 (68%)	57	77	0.73[e]
Anatomic location uveitis (n (% of total))				**0.02**[e]
Anterior	135 (69%)	66	69	
Intermediate	21 (11%)	6	15	
Posterior	8 (4%)	0	8	
Pan uveitis	32 (16%)	13	19	
Median LogMar visual acuity at diagnosis (IQR)	0.22 (0.11 to 0.60)	0.22 (0.03 to 0.60)	0.22 (0.01 to 0.70)	0.61[a]
Ocular complicatons (n (% of total))[f]				0.11[c]
No complications	56 (29%)	24	32	
Anterior complications[g]	66 (34%)	36	30	
Posterior complicatons[h]	36(18%)	11	25	
Anterior and posterior complications	36(18%)	14	22	
Etiology (n (% of total))				**< 0.001**[c]
E.c.i	81 (41%)	28	53	
JIA[i]	92 (47%)	53	39	
HLA-B27	6 (3%)	3	3	
infectious	11 (6%)	1	10	
Other auto-immune	6 (3%)	0	6	
ANA[j] positive	104 (57%)[i]	53 (62%)	51 (46%)	0.07[c]
IOP[l] **measurements** (mmHg), (median, (IQR))				
First IOP measurement	16 (13 - 20)	16 (14 - 22)	16 (13 - 19)	0.11[a]
IOP disease remission	19 (15 - 23)	21 (17 - 27)	18 (15 - 21)	**0.002**[a]
Highest IOP during FU[m]	32 (24.5 - 38)	37 (34 - 42)	27 (20 - 32)	**< 0.001**[a]
Time measurements (months, (median, (IQR))				
Time to disease remission[n]	6 (3 - 12)	5 (3 - 10)	6 (3 - 14)	0.23[a]
Time to highest IOP during FU[o]	17 (6 - 41.5)	28 (10 - 52)	13 (3 - 36)	**0.004**[a]
Time to start glaucoma medication	6 (1 - 21)	5 (1-21)	9 (1-25)	0.33[a]
Time to glaucoma surgery	N/A[p]	31 (12-54)	N/A[p]	
Median FU	86 (43 - 144)	114 (71 - 180)	66 (37 - 115)	**< 0.001**[a]
Additional treatment (n (% of total))				
Systemic immune- suppression				
At start uveitis[q]	71 (36%)	24	47	**0.04**[c]
During follow up[r]	160 (82%)	71	89	0.47[c]
Cataract surgery	102 (52%)	68	34	**< 0.001**[c]
Cataract surgery before glaucoma surgery[s]	65 (33%)	31	34	0.39[c]
Maximum glaucoma medication used (n)	5	4 (4 - 5)	1 (0 - 2)	**< 0.001**[a]
> 2 types of glaucoma medication n (% of total))	107 (54%)	83	24	**< 0.001**[c]

[a] Mann-Whitney, [b] interquartile range,[c] Center 1 = University medical center Groningen. From this center, all cases and controls were included. [d] Center 2= University medical center Utrecht. All cases were included and 48 randomly chosen controls were included. [e] Pearson chi-square, [f]missing n=2, [g]anterior complications: *Band keratopathy, cataract, posterior synechiae*, [h] posterior complications : *Macular-edema, papillitis*, [i]Juvenile idiopathic arthritis, [j]Anti nuclear antibodies, [k] missing n=12, [l] IOP = intra ocular pressure, [m] FU = follow up, [n]missing n=42, [o]missing n= 2, [p] N/A = not applicable, [q]missing n=1, [r] missing n=2,[s] cataract surgery longer than 3 months before glaucoma surgery

Anterior location of the uveitis and JIA related uveitis were significantly more frequently present in the cases (78% versus 62%, P=0.02 and 62% versus 35 %, P<0.001), respectively). At presentation, anterior ocular complications tended to be more frequently observed in the cases, but this difference was not statistically significant (59 % versus 47 %, P=0.1). ANA-positivity tended to be, although not statistically significant, more frequently found in the cases (62% vs 46%, P=0.07). The cases used more often more than two different types of glaucoma medication during the follow-up (83% versus 25%, P<0.001) and 70% of the cases underwent glaucoma surgery within 1 year after increasing the number of glaucoma medication to three or more types (Table 2).

Table 2. Cumulative number of patients operated for glaucoma[a]

Time to surgery	Number (%) of patients [b]
< 1 year	58 (70%)
< 2 years	65 (78%)
< 3 years	72 (87%)
< 4 years	77 (93%)
< 5 years	79 (95%)
< 6 years	80 (96%)

[a] Cases using more than two types of glaucoma medication are displayed. In the controls 24 patients used more than two types of glaucoma medication. [b] In 3 cases data on time to glaucoma surgery are missing and 2 cases used ≤ 2 types of glaucoma medication

Median (IQR) follow up time overall was 86 (43–144) months with a longer follow up time in the cases (P<0.001). Overall, cataract surgery was performed more frequently in the cases (67% vs 31%, P<0.001). If only cataract extractions performed >3 months prior to glaucoma surgery were included in the analysis, no differences were found between cases and controls.

Patient data differed between centers. The total cohort of patients included from the UMC Utrecht (Center 2) as compared to the UMC Groningen (Center 1) were younger (P=0.04), had more frequently a JIA-related uveitis (P=0.02), had more frequently an anterior uveitis (P=0.005) and less patients suffered from posterior complications (P=0.001). Cox proportional hazards regression analysis was used as a predictive model for time-to-event data. After accounting for the confounding effect of center, we found that anterior uveitis (HR 2.1 (95% CI 1.0 to 4.2); P=0.04) and higher IOP at presentation (HR 1.05 per mmHg (95% CI 1.0 to 1.1); P=0.02) were independently and significantly associated with a higher risk of glaucoma surgery (supplement data: Table 3). A survival curve was graphically displayed for the mean of covariates in the entire patient group (Figure 1).

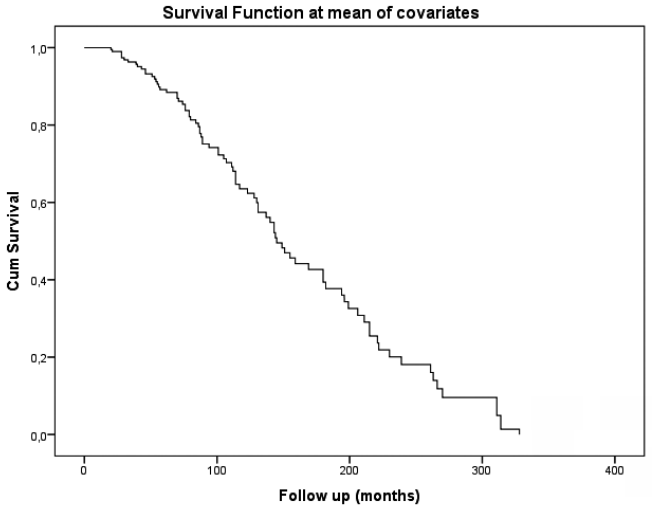

Figure 1. Survival-curve at mean covariates for the entire patient group. The relationship between the influence of multiple risk factors on the probability of glaucoma surgery is displayed for the entire patient group. The horizontal axis shows the time to glaucoma surgery, the vertical axis shows the probability of survival. The shape of the survival function is estimated from all observed subjects.

DISCUSSION

In this study with 196 pediatric uveitis patients, we show that the risk of glaucoma surgery is highest in children with anterior uveitis. Our data also indicates that in the majority of the cases glaucoma surgery is required within a year after a third type of glaucoma medication is prescribed. In patients with uveitis onset at younger age, JIA-related uveitis and patients with higher IOP during follow up, statistically significantly more glaucoma surgery is performed. Known risk factors from the literature such as ANA positivity, female predominance and anterior complications[12], are not confirmed in our study.

In our multivariate Cox survival analysis, after adjusting for other covariates, only anterior uveitis and IOP at diagnosis are independently and significantly associated with a higher risk of glaucoma surgery. Anterior uveitis is a known risk factor for the development of ocular hypertension and glaucoma[7,8,12–15]. Also, for the treating ophthalmologist, anterior uveitis is a clearly identifiable risk factor, whereas IOP at presentation is much less clinically relevant, since median IOP (16 mmHg) did not differ between the cases and controls. Although anterior uveitis is most frequently found in the cases, the presence of anterior complications at diagnosis such as band keratopathy, cataract, or posterior

synechiae are not related to a higher risk of glaucoma surgery in our study (P=0.1), which contradicts the literature[7,8,12–15].

During follow-up, additional risk factors were identified by univariable analyses (Table 1). Of these, requirement of a third type of glaucoma medication can be considered as a tipping point, since it indicates the need of glaucoma surgery within a year in the majority of the cases. (Table 2). More frequent monitoring of IOP and compliance to glaucoma medication are recommended for these children. Also, early referral to an ophthalmologist specialized in glaucoma-surgery is advised to prevent a delay in surgical treatment of glaucoma.

In our study, patients who require glaucoma surgery are younger at the time of uveitis diagnosis. This may indicate a more severe disease and inherent complications due to prolonged disease and treatment with topical steroids[13,16]. There is no consensus in the literature regarding this aspect, since some previous studies agree[8,13], but others report older age at onset of the uveitis to be related to ocular hypertension or secondary glaucoma[12].

More patients with JIA-uveitis were found among the cases when compared to the controls (53 (58%) vs 39 (42%), P=<0.001). In the literature, the prevalence of glaucoma in JIA-associated uveitis has been reported to range from 14 -40%[12]. JIA-related uveitis is most commonly anteriorly located, chronic and most patients are treated in a uveitis expertise center. We included patients from two tertiary centers, of which the UMCU is an academic expertise center for patients with JIA. This possibly explains the relatively higher need of glaucoma surgery in the JIA subgroup when compared to the literature[7,13].

In our study, topical, subconjunctival as well as systemic anti-inflammatory medication are widely used mostly during the whole follow-up. Increasing IOP due to steroid-response induced by topical steroids may therefore play an important role, despite the careful prescription of local steroids and a maximum daily maintenance dose of 3 times per day. In children, the ocular-hypertensive response to topical steroids occurs more frequently, severely and rapidly than in adults[1,17,18]. Elevation of IOP can be found in most patients as early as the first or second week[19,20]. In our study, the highest IOP during the follow-up is measured after 28 months in the surgery group and 13 months in the control group with a large variation in time. This relatively late increase in IOP in both groups is a combined result of changes in the trabecular system, the ocular-hypertensive response to topical steroids, and adaptations in glaucoma medication during follow-up. Thus reflecting the multifactorial pathophysiology of increasing IOP in uveitis.

In some papers, previous cataract surgery is related to the severity of the uveitis and a higher risk of uveitic glaucoma[12,16]. In our data, the proportion of cases that underwent cataract surgery before glaucoma surgery was not statistically significantly different from that of controls. During the entire follow-up, more cataract surgery is performed in the cases than in the controls (68% versus 34%, P<0.001). The development of cataract is probably based on the impact of glaucoma surgery and the long-term use of medication to control the uveitis[19,21].

To analyze the differences between the two groups at diagnosis and in the course of the disease, we followed the patients as long as possible. The follow-up is shorter in the controls when compared to the cases, partly because of a loss to follow-up due to a stable course and therefore a return to the referring ophthalmologist. With a different follow-up duration in cases versus controls of 9 years versus 6 years, it is likely that there are patients in the control-group who will need glaucoma surgery in the future.

Various surgical techniques are possible for treating glaucoma in childhood[22,23]. Glaucoma surgery is still a challenge for the ophthalmologist and far-reaching for the child. In this patient group, it is essential to perform surgery on time, but choosing the optimal moment is difficult. Weighing the chance of irreversible visual loss due to glaucomatous damage against that from complications induced by glaucoma surgery are difficult considerations[22]. The changes in eyesight, uncertainty about the disease course, necessary changes in medication and frequent school absence due to monitoring visits to the ophthalmologist may have a strong impact on the quality of life of a young patient and their parents[24]. Finding a balance between prevention of irreversible loss of vision due to glaucoma and reducing the iatrogenic impact on a child's quality of life is a challenge encountered in all cases.

In our study, we combined data from the UMCG and the UMCU. Our cox-regression analysis showed a significant differences between the two centers (supplement data: Table 3). This differences are meanly based on differences in patient population, due to the specialized health care in treating JIA patients at the UMCU and the responsibility for specialized and more general care of uveitis patients during the study period at the UMCG.

The results of the current study are limited by the fact that the study is retrospective, there is a large variability in follow up time and data-imputation was performed for variables with missing data. All patients were included from two tertiary centers in the Netherlands and therefore do not represent the total spectrum of pediatric uveitis. Also, personal experience or preferences of ophthalmologists and pediatric rheumatologist may have influenced the choice and course of treatment. The strengths of this study are its cohort size,

the systematic way in which data were collected, its adherence to the SUN classification system and guidelines for publications[9–11] and the sharing of expertise in a difficult and challenging patient population.

CONCLUSION

This study on the risk factors for developing medically uncontrollable high intraocular pressure in pediatric uveitis is one of the largest currently available in the literature. The authors emphasize the importance of careful treatment and monitoring in pediatric uveitis patients with anterior uveitis, JIA-related uveitis and in patients who are already treated with more than two types of glaucoma medication. Adequate monitoring, risk assessment and early referral to a glaucoma specialist experienced in this patient group is recommended.

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Supplement data: Table 1. Variables with ≥ 10% missing data

Missing (n(% of total)	Total	Center 1	Center 2	P-value[a]	Cases	Center 1	Center 2	P-value[a]	Controls	Center 1	Center 2	P-value[a]
First IOP measurement	40 (20%)	23	17	0.2	18	7	11	0.9	22	16	6	0.09
IOP disease remission	39 (20%)	22	17	0.3	22	8	14	0.6	17	14	3	**0.02**
Time to disease remission	42 (21%)	24	18	0.2	23	10	13	0.7	19	14	5	0.1

[a] Pearson chi-square

Supplement data: Table 2. Imputed data[a]

Variables	Original data (mean, SD)	Pooled data (mean, SEM)
First IOP measurement (mmHg)	16.9 (± 6.1)	16.9 (0.5)
IOP disease remission (mmHg)	19.9 (± 7.7)	20 (0.6)
Time to disease remission (months)	9 (± 9)	9.5 (0.7)

[a] Multiple imputation by Linear Regression. Missing data was missing at random (MAR) (Little's MCAR test: P =0.006). Thirteen cases with missing data on all three variables were excluded from data-imputation. Variables with missing data on < 3 variables were used as predictors for imputation. Constraints were set based upon observed minimum and maximum values found within the variables. Number of imputations: 20.

Supplement data: Table 3. Outcome Cox-regression analysis in original and imputed data. P-value < 0.1[c]

Variables[c]	Original [a]	1[b]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	11[b]	12[b]	13[b]	14[b]	15[b]	16[b]	17[b]	18[b]	19[b]	20[b]	21[d]
Center	0.04	0.04	0.04	0.02	0.02	0.06	0.03	0.04	0.05	0.03	0.02	0.04	0.06	0.02	0.02	0.04	0.03	0.03	0.02	0.04	0.02	0.02
Age at onset uveitis (yrs)			0.09	0.06	0.06		0.06				0.06			0.06			0.09	0.07	0.05		0.06	
Anterior location uveitis	0.02	0.06	0.08			0.09		0.06	0.05	0.08		0.06	0.08		0.05	0.06						0.04
JIA																						
ANA																						
Anterior complications																						
First IOP measurement (mmHg)	0.02	0.005	0.07	0.005	0.05	0.003	0.02	0.003	0.06	0.01	0.05	0.05	0.005	0.02	0.002		0.02		0.07	0.01	0.09	0.02

[a] Original database, [b] Imputed dataset, [c] Variables with significance level P < 0.1 are presented, [d] Mean imputed.

8

FUTURE PERSPECTIVES

CAN VISUAL OUTCOME AND TREATMENT IN SCLERITIS BE IMPROVED?

Recent papers on the outcome of patients with scleritis [1, 2] do not report better visual outcomes than the results presented in our study. Improvement of visual outcome depends on early recognition, adequate assessment of the severity and tailored treatment of the scleritis and its complications. Early recognition can sometimes be difficult in posterior scleritis causing delay in diagnosis and treatment [3, 4]. For diagnosing posterior scleritis, ultrasound is necessary. Performing and interpreting ultrasound is not a standard competence of every ophthalmologist. Recent developments in easy and accessible imaging such as enhanced depth OCT may improve diagnostics in posterior scleritis [5, 6]. Studies on the immunopathology of necrotizing scleritis provide insight in the disease mechanism and perhaps a chance of more effective treatment [7, 8]. Studies on histopathological specimens, usually with chronic and severe end stage disease have revealed four types of scleritis, each with different disease associations, involved cell types, immune complexes and cytokines [7 - 10]. New treatments should be based upon the improved understanding of the immuno-pathogenesis and should ideally be targeted at specific mediators and cells of the immune system and be as local as possible. Still, almost all cases of scleritis need systemic treatment, although the temporally positive effect of subconjunctival injections with local steroids has been described [11, 12]. The deliberate use of financial resources in health care should also be considered in treating patients with scleritis. The optimal use of older proven medications such as methotrexate is of benefit for patients because effect and side-effects are well-known [13, 14] and in many cases these medications are cheaper than newly developed drugs. A number of attempts have been made to develop and validate a clinically applicable grading system for the severity of scleritis [15, 16]. In our study, these grading systems could not be validated. Recent, another simplified grading system was proposed but not validated [17]. In the busy clinical ophthalmology practice, a clinical assessment should be practical and quick. The clinical picture, the severity of the patients complaints, the presence or absence of an underlying systemic disease and the necessary additional investigations should ideally guide diagnosis, treatment and thus prognosis. Questions such as how long treatment should be continued before dosage is tapered or treatment can be stopped still remain unanswered.

THE GREAT MASQUERADER STRIKES AGAIN. REMAINING QUESTIONS REGARDING OCULAR SYPHILIS.

Does HIV positivity have an impact on presentation, outcome and prognosis of ocular syphilis?

In earlier publications on ocular syphilis, HIV positivity has been associated with a more posteriorly located uveitis, neurosyphilis and a worse visual outcome [18 - 21]. These findings could not be confirmed by us and other recent studies [22 - 25]. This is probably due to the improved treatment and immune status of HIV-positive patients in which they react and respond similar to infection and treatment as HIV negative patients. This is in line with current IUSTI guidelines which state that HIV co-infected syphilitic patients should be treated as immunocompetent patients, except for those who have CD4+ cell counts of ≤ 350/μL [26].

What is the relationship between ocular syphilis and neurosyphilis?

There is an ongoing debate as to whether ocular syphilis should be classified as neurosyphilis. In particular in isolated anterior uveitis, with involvement of structures that are embryonically not derived from the neuroepithelium [27]. Some suggest that structures derived from the neuroepithelium should be regarded as part of the brain and therefore retinitis and optic neuritis should be classified as neurosyphilis [24,28]. Others suggest that involvement of any eye structure, irrespective of its embryogenesis, should be managed identically to neurosyphilis [24, 28]. This advice is adopted by the current guidelines on the treatment of ocular syphilis [26] wherein- regardless of the anatomical location of the uveitis - a treatment regimen identical to that of neurosyphilis is advised. The diagnosis of neurosyphilis depends on a combination of positive serologic test results, neurologic signs and symptoms and cerebrospinal fluid (CSF) abnormalities [26, 27]. Up to 60% of patients with ocular syphilis will have cerebrospinal fluid (CSF) abnormalities [27] and there is no definite evidence that anterior uveitis is associated with a decreased risk of having abnormal CSF compared with posterior uveitis [24]. CSF examination can be helpful in the differential diagnosis by excluding other pathologies and if found to be abnormal and consistent with neurosyphilis, appropriate follow-up to ensure all markers return to acceptable levels is required [26].

Can syphilis screening and confirmatory tests be improved?

For syphilis screening, serologic tests are used. If a screening test is found to be positive, a confirmatory test, in most cases an enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA) or immunoblot is used [26]. Different tests are available for the diagnosis and staging of syphilis. Untreated syphilis is divided into four stages, ocular syphilis may occur in all stages, except in the primary stage. Serologic screening tests are divided into nontreponemal and treponemal tests. Nontreponemal are not specific for treponemal infection and are generally used to monitor responses to treatment or to indicate new infections in patients

with possible syphilis re-infection. False-positive nontreponemal tests have been associated with multiple conditions [29] and nontreponemal test results might be falsely negative in longstanding latent infection [30]. Treponemal tests, which are based on antigens derived from T. pallidum, have higher sensitivity and specificity than nontreponemal tests. However, because treponemal antibodies may survive a lifetime after infection, they cannot distinguish between current infection and past infection and they cannot be used for evaluation of therapeutic effect [29]. Analysis of ocular fluid for treponemal DNA has been reported to be helpful for diagnosis in some case reports [31-34]. However it is not well-validated for aqueous and vitreous humor and neither sensitivity nor specificity are clear [31]. Ongoing research is aimed at developing new generations of immunotests with advanced diagnostic capabilities which will hopefully be able to detect immunoreactivity in different syphilis stages and a decreasing immune response after the infection regresses [35].

DEVELOPMENTS IN UNDERSTANDING OF THE PATHOGENESIS AND POSSIBLE THERAPEUTIC APPROACHES IN RETINAL DYSTROPHIES

Retinal dystrophies are a rare group of retinal diseases and a major cause of incurable blindness in the western world. Retinal dystrophies have remained largely untreatable due to the challenges posed by their genetic heterogeneity and due to lacunae in the understanding of the mechanisms of these diseases [36]. Recent developments in research have improved knowledge of the pathogenesis and mutations in over 200 genes are now known to be involved in the pathogenesis of this group of diseases [36]. Several pathways of disease are likely to be involved in retinal dystrophies depending on the genes involved, and may require different therapeutic approaches for genetically different groups of patients [37]. Therapeutic approaches that are being explored in clinical trials include dietary supplements of carotenoids and related compounds to promote retinal function [38, 39] administration of neurotrophic factors [40 - 42] gene replacement therapy [43 - 47], and the use of prosthetic devices [48, 49]. Some of these trials have so far indicated safety and efficacy in humans of the treatments tested [36, 38 - 49]. These results are promising and future challenges in research and treatment are focused on further unraveling of the heterogenic disease mechanisms and safety and efficacy of its possible treatments.

THE ROLE OF MTX IN THE ERA OF EXPANDING TREATMENT OPTIONS IN PEDIATRIC NON-INFECTIOUS UVEITIS

For decades, MTX monotherapy has been the cornerstone of systemic treatment for auto-immune ocular inflammatory disease (OID) [13, 14, 50]. This is mainly based upon its well-known safety profile and its effectiveness in about 70 % of patients with OID [14, 50]. Treatment options for patients suffering from auto-immune OID

disease have expanded profoundly over the last decades and have been proven safe and effective [51-53]. In the treatment of adult rheumatoid arthritis (RA) patients there are concerns that since the introduction and advent of TNF inhibitors MTX is less aggressively dosed, duration of use is shorter and a more rapid escalation to biologicals is made [54, 55]. This was confirmed by a large study performed in adult RA patients [56]. In this study, a large part of the patients switched to other, more expensive treatments with less well known efficacy and long term safety. In children with non-infectious uveitis, ineffectiveness or side effects are common reasons for switching to other forms or treatment. If side effects such as nausea, needle phobia or elevated liver enzymes can be managed, MTX treatment can be continued. The frequency and consequences of MTX-induced nausea has probably the greatest impact in clinical practice and frequently leads to non-adherence or discontinuation of MTX [57-59]. Gastro intestinal (GI) related symptoms in children with JIA and treated with MTX can be evaluated with the Methotrexate Intolerance Severity Score (MISS) [58] or the Gastrointestinal Symptom Scale for Kids (GISSK) [60]. In some cases, switching to oral or subcutaneous administration solves the GI symptoms. In others patients, co-medication with anti-emetics or behavioral interventions for MTX-induced anticipatory nausea can be tried. In case of ineffectiveness, a switch to another medication is inevitable, although this can sometimes be combined with a lower dose of MTX in combination with another route of administration. This concomitant use of MTX during treatment with certain TNF-α inhibitors has been demonstrated to decrease the formation of antidrug antibodies (immunogenicity) [61]. These anti-drug antibodies can be functionally neutralizing and thereby directly affect treatment efficacy. Prevention or reduction of immunogenicity, results in higher systemic exposure and enhanced clinical efficacy [62-64]. Next to that, combination therapy may enable dose reductions of individual agents, thereby decreasing toxicity and improving tolerability and compliance [61]. MTX remains the anchor DMARD (disease modifying anti rheumatic drug) for OID, it is effective, well-tolerated, economical and universally recommended by all treatment guidelines and it can optimize treatment with TNF-α inhibitors[50-52, 56,61, 65, 66].

A HOLISTIC APPROACH IN THE TREATMENT OF PEDIATRIC UVEITIS

Patients with chronic diseases are suffering from the direct and indirect consequences of their disease [67]. Physical and psychosocial consequences not directly related to the disease are of importance for assessment and comparison of the level at which a patient is functioning despite their illness. Treatment goals in chronic disease should therefore include patient reported outcomes with regard to physical and psychosocial functioning next to satisfactory medical outcome. Questionnaires used for testing quality of life (QoL) should incorporate questions addressing visual function for testing vision related QoL and these questionnaires

should be suitable and validated for use in children with uveitis [68, 69]. In roughly 40 % of the children, the uveitis is related to JIA. From the literature, we know that patients with JIA and other chronic diseases are physically less active and have reduced physical fitness levels [70, 71]. Also, lower health-related quality of life (HR QoL) and more fatigue is reported for adult and pediatric patients with uveitis and other auto-immune diseases [68, 69, 72 -82]. Further, it is known that in auto-immune disease physical activity performed in the appropriate way is safe, improves QoL, decreases fatigue and has a number of positive effects on the immune system [83]. Further research focused on the pathophysiology of non-infectious uveitis is needed to assess whether the inflammation in uveitis is really limited to the eye or may extend itself systemically and on what aspects JIA-patients with uveitis are different from JIA-patients without uveitis [79, 84]. Finally, children with uveitis are treated in a multidisciplinary approach. Patients and their parents benefit from optimal communication between all involved physicians [65] Next to that, creating awareness for a healthy lifestyle, encouraging hobbies or sports activities and being a role model are recommended for every involved physician.

DEVELOPMENTS IN PEDIATRIC UVEITIC GLAUCOMA

In uveitic glaucoma, IOP's are generally unacceptable high on maximal medication and the only solution to prevent irreversible visual loss or blindness is glaucoma surgery. Anatomical and biochemical changes in the anterior part of the eye related to the inflammation and its treatment are responsible for the rise in IOP. An important factor is the ocular-hypertensive response to topical steroids. This response is well documented in children and is known to occur more frequently, severely and rapidly than reported in adults [85, 86]. Unfortunately, avoidance of topical steroids is in most cases no option because alternative eye drops with equal effectiveness are currently not available [87]. Other, more experimental, local treatment alternatives such as MTX, infliximab and sirolimus should be administered by frequent intravitreal injection. [88 - 92]. This route of administration is much more invasive and too little is known about efficacy and safety. This in contrast to systemic immune suppression wherein safety and efficacy have been shown extensively [93, 94]. In one study, a delay in time to necessary cataract extraction with 3.5 years is reported in patients treated early with systemic MTX [95]. But, evidence supporting starting or increasing systemic immune suppression in an attempt to reduce topical steroids and thus reducing or preventing the ocular-hypertensive response to topical steroids is lacking in the current literature. As shown in our study and by others, children with JIA-uveitis [96,97] are more prone to develop secondary glaucoma. Recent studies suggest that neuro-inflammation is a contributing factor for glaucomatous neurodegeneration [98, 99]. It is suggested that IOP elevation can activate inflammatory responses and production of cytokines and chemokines especially by microglia [98, 99].

Microglial activation is reported to be one of the first events in glaucomatous neural damage occurring prior to retinal ganglion cell loss [100,101]. This neuro-inflammatory reaction shows overlap and similarities with reported neuro-inflammation in autoimmune conditions[102]. These findings support the theory that neuro-inflammation increases the occurrence of glaucoma in patients with JIA-uveitis. Further research is necessary to unravel these disease pathways and possible treatment options. A number of different surgical techniques are used in the surgical management of medically uncontrollable high IOP. The traditional procedure of first choice is a trabeculectomy [103]. If trabeculectomy fails or is not possible, aqueous shunts such as Ahmed, Baerveldt or Molteno implants can be used. In the literature, slightly lower IOP and lower complication rates are reported for the Baerveldt implant when compared to trabeculectomy and Molteno and Ahmed implants [103 - 105]. Recent publications in small groups of uveitis patients report positive results from angle surgery procedures like goniotomy and trabeculotomy [106 - 108]. The latter have the advantage that in case of ineffectiveness or complications they can be followed by implant surgery. Next to that, in angle surgery systemic immune suppressives can be continued. In contrast, in our clinic, patients who are planned for glaucoma implant surgery are advised to stop MTX two months prior to surgery, because MTX gives a higher chance of hypotonia due to less marked encapsulation of the implant. This procedure is based upon our own clinical experience of postoperative hypotonia and on the results of in vitro studies showing that MTX inhibits the proliferation of fibroblasts and induces their apoptosis [109 - 116]. Developments and insights in disease mechanisms, pharmacological and surgical treatments in pediatric uveitis glaucoma are promising. But, the disease course and its treatment remain complex and challenging for the clinician, patients and their parents.

In conclusion, the results of the research presented in this thesis emphasize the need for a tailored and multidisciplinary treatment approach in inflammatory eye diseases. Ideally, treatment should be based upon disease mechanisms, location of the inflammation, necessary treatment of ocular complications, presence of underlying systemic disease, effectiveness and side-effects of medication, effects on general well-being and functioning, judicious use of available financial resources and individual patient characteristics.

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9

APPENDICES:

SUMMARY

NEDERLANDSE SAMENVATTING

CURRICULUM VITAE

DANKWOORD

LIST OF ABBREVIATONS

SUMMARY

In the six studies presented in this thesis, several challenges on both the diagnostic and therapeutic aspects in the treatment and counseling of patients with inflammatory eye disease are addressed. The first part of this thesis consists of three studies aimed at improving the diagnostic and therapeutic process in adult patients with inflammatory eye diseases of different etiology, prognosis and treatment. In the second part, three studies are presented that investigate some challenges that are encountered in the treatment of inflammatory eye disease and its complications in children. In this closing chapter the results of the different studies are summarized and future perspectives are discussed.

In **chapter 2** the outcome, treatment results and prognosis in a cohort of 104 patients with scleritis are presented. This study is - just as the five other studies in this thesis - retrospective in nature. This approach gives the second lowest level of scientific evidence and is often the only methodology available and ethically allowed for rare and threatening diseases. In our study, the visual outcome of patients with scleritis was generally good with the exception of necrotizing and posterior scleritis. Treatment was administered by a stepladder approach based upon etiology, severity of the scleritis and the presence of an underlying systemic disease. In 47 patients, treatment with steroid-sparing immunosuppressive medication was started, in most cases MTX followed by MMF. In 11 patients, after failure of MTX or MMF, treatment with tumor necrosis factor α (TNF-α) antagonists was started. Globally in our study, for each steroid-sparing immunosuppressive drug, treatment success was achieved in approximately half of the patients. Azathioprine seemed to be an exception, because this drug seemed less effective in our study. Within this patient group, necrotizing scleritis, male gender, a longer duration of symptoms at presentation, systemic disease, and bilateral disease at any time indicated a worse prognosis. In multivariate analysis, bilateral disease at any time was the strongest independent predictor associated with a more severe disease course.

In **chapter 3** we report on the visual outcome, effectiveness of various modes of antibiotic treatment, and prognostic factors in 85 patients with serologically proven syphilitic uveitis treated in 5 different tertiary uveitis centers in The Netherlands. In this study, the overall visual prognosis was good if timely and adequate therapy was given, although 6 patients with structural damage to the optic nerve and retina suffered from severe visual loss. Improvement in visual acuity 6 months after initiation of antibiotic treatment was found in all treatment modalities. Some non-intravenous treatment subgroups had modest size, but no statistically significant differences were found in visual acuity at 6 months

follow up in multivariable analysis. In multivariable analysis, patients treated with intravenous penicillin showed a tendency towards a better visual acuity at 6 months follow up. We could not comment on the beneficial or adverse effects of additional oral steroids or steroid injections because corticosteroids were likely to have been preferably given to the more severe cases. Prognostic factors were analyzed in relation to visual outcome at 6 months. In this analysis, a low visual acuity at presentation and a treatment delay of more than 12 weeks were both independently associated with a less favorable visual prognosis.

In **chapter 4** the diagnostic process, clinical characteristics and outcome of 6 patients from 3 different tertiary uveitis centers in The Netherlands with genetically confirmed retinal dystrophy presenting as intermediate uveitis (IU) with cystoid macular edema (CME) are reported. All 6 patients presented themselves with suboptimal visual acuity and intermediate uveitis with CME. Their IU was subsequently classified as idiopathic based upon a negative diagnostic workup by a rheumatologist or immunologist. In none of the six patients obvious clinical signs of retinitis pigmentosa were found on presentation or during follow up. Treatment with immune - suppressives was commenced in 5 patients. Additional testing of visual field was performed, which showed varying degrees of peripheral visual field loss. During follow up CME persisted, peripheral visual field loss progressed and 3 patients reported nyctalopia. Also, in all patients full field electroretinograms (ERG) were performed and showed reduced scotopic and photopic responses. Systemic immune suppressive treatment did not reduce the CME or inflammation and did not improve visual acuity. The disease course led to the reconsideration of diagnosis and retinal dystrophy was suspected. Diagnosis of retinal dystrophy was confirmed in all patients by DNA screening for known DNA mutations related to retinal dystrophies. A mutation in the CRB1 gene was found in 3 patients, 1 patient had a mutation in the RP1 gene, 1 patient had a mutation in the USH2A gene, and 1 patient had 2 dominant RD genes. Considering the outcome in these 6 patients, retinal dystrophy should be included in the differential diagnosis of patients with therapy resistant intermediate uveitis with CME on OCT. Furthermore, in these patients we advise direct questioning of nyctalopia and family history of retinal disease, testing of peripheral visual field, measuring of full-field ERG and counseling by an ophthalmologist with expertise in the field of retinal dystrophies. Timely recognition and thus early diagnosis prevents unnecessary treatment with immune – suppressives and allows adequate counseling in this patient group.

Chapter 5 is the first chapter of the second part of this thesis. In this second part the results of the studies in children are reported. In chapter 5, the study on the comparison of efficacy of high and low dose methotrexate in 42 children with non-infectious uveitis is presented. Outcome measures are time to disease

remission, steroid-sparing effect and side effects. This study shows that patients who are treated with a high dose of MTX (≥15mg/m^2/week) reach remission on medication sooner when compared to patients who are treated with a low dose of MTX (<15mg/m^2/week). The data also indicates that an MTX dose of ≥15mg/m^2/week administered by subcutaneous injection is the most effective in establishing rapid remission on medication. The sample size in the patients treated with highly dosed oral MTX is small and is therefore not commented on. Visual acuity measurements at 6 and 12 months show a better outcome in the group treated with high dose MTX. But, later in the follow up visual outcome between high and low dose groups is comparable. High and low dose groups are equal to each other with regards to severity of uveitis, incidence of ocular complications and surgery, steroid sparing capacity of MTX, cumulative dose of MTX and side effects. Based upon our results, the best available evidence from the treatment of rheumatoid arthritis and our own clinical experience, an MTX starting dose of ≥15mg/m^2/week by subcutaneous administration with a maximum of 25 mg/week is recommended in the treatment of pediatric non-infectious uveitis. After reaching remission on medication a lower (10-15 mg) – possibly oral – maintenance dosage can be considered to maintain remission. This treatment strategy hopefully leads to shorter disease duration, prevention of visual loss and ocular complications and to rational use of the different treatment options in these patients.

In **chapter 6** we present the results of our pilot study on physical fitness, physical activity and psychosocial health in 23 children treated for uveitis at our center. Initially, 42 patients were eligible for the study, after exclusion of 1 patient, 23 patients were willing to participate. In these 23 patients, levels of cardio-respiratory fitness, physical activity, muscle strength, health-related quality of life and fatigue were studied. Mean weight and body mass index (BMI) of the patients were statistically significantly higher when compared to the reference population. The 10 patients with juvenile idiopathic arthritis (JIA) -associated uveitis had a significantly higher BMI than the 13 patients with idiopathic uveitis. Physical fitness was measured by exercise capacity and muscle strength. Exercise capacity was, although not statistically significant, lower than the reference values of healthy children. Muscle strength was in comparison to healthy controls, statistically significantly reduced in our group of patients. No differences in physical fitness between JIA-related and idiopathic uveitis were found. All children with uveitis were statistically significantly less physically active when compared to their healthy peers and no differences were found between JIA and idiopathic uveitis patients. Health related quality of life (HR QoL) and fatigue were addressed by questionnaires which consisted of a child self-report and a parent proxy report part. Children themselves reported normal HR QoL and fatigue. Parents reported that their children have a statistically significantly lower HR QoL and more fatigue when compared to parents of healthy children. In

conclusion, in this study we show that patients with non-infectious uveitis are at risk of developing cardiovascular risk factors early in life. Children with uveitis have a higher BMI, lower cardio-respiratory fitness and are less physically active when compared to healthy peers. Furthermore, their parents report a lower quality of life and more fatigue for their children compared to the parents of healthy children. Children with idiopathic non-infectious uveitis had similar test results as children with JIA-uveitis, so it remains undecided whether these results can be attributed to the systemic treatment or the inflammatory disease. Treatment of pediatric uveitis should be aimed at improving the physical and psychosocial health and reducing cardiovascular risk factors in this vulnerable group of patients in addition to maintaining and preserving vision.

In **chapter 7** the results of our study on the risk factors for the development of secondary glaucoma needing glaucoma surgery are reported. The study was conducted in a cohort of 196 pediatric uveitis patients from 2 tertiary uveitis centers in the Netherlands. The aim of this study was to identify risk factors of raised intra ocular pressure (IOP) needing glaucoma surgery in a large group of children with uveitis. In this study, 85 patients underwent glaucoma surgery. At uveitis onset, patients in the surgery group as compared to the non-surgery group were younger (median age 6 versus 8 years, P=0.008), uveitis was more often located anteriorly (78% versus 62%, P=0.02), and was predominantly associated with JIA (62% versus 35%, P <0.001). During follow-up, patients in the surgery group underwent cataract surgery more often (80% versus 31%, P < 0.001), had higher maximum intra ocular pressures (IOP) (IOP 37 mmHg versus 27 mmHg, P <0.001) and more often used more than 2 types of glaucoma medication (83% versus 24%, P <0.001). To identify possible risk factors, covariates present at presentation were included in a multivariable Cox survival analysis. We found that anterior uveitis and a higher IOP at presentation were independently and significantly associated with a higher risk of glaucoma surgery. Next to that, patients who needed more than 2 types of glaucoma medication were likely to need glaucoma surgery in the nearby future. Early referral to a glaucoma specialist experienced in pediatric glaucoma surgery may contribute to the early detection of the need for glaucoma surgery in this patient group, thus enabling surgery at an early stage of the disease and the prevention of irreversible damage. Careful treatment and monitoring in pediatric uveitis patients with anterior uveitis, JIA-related uveitis and in patients who are already treated with more than two types of glaucoma medication is recommended.

NEDERLANDSE SAMENVATTING

In de onderzoeken die in dit proefschrift worden gepresenteerd, komen verschillende uitdagingen op het gebied van diagnostische en therapeutische aspecten in de behandeling van patiënten met inflammatoire oogziekten aan de orde. Het eerste deel van dit proefschrift beslaat drie onderzoeken gericht op verbetering van het diagnostisch en het therapeutisch proces bij volwassen patiënten met inflammatoire oogziekten van verschillende etiologie, prognose en behandeling. In het tweede deel worden drie studies gepresenteerd aangaande de behandeling van inflammatoire oogziekten en bijkomende complicaties bij kinderen.

In **hoofdstuk 2** worden de uitkomsten, behandelresultaten en prognose gepresenteerd van het onderzoek wat verricht werd onder een groep van 104 patiënten met scleritis. Deze studie is – net als 4 andere studies in dit proefschrift – retrospectief opgezet. Deze opzet geeft het op één na laagste niveau van wetenschappelijk bewijs, maar is vaak de enige methode beschikbaar die medisch ethisch verantwoord is voor zeldzame en bedreigende aandoeningen. In onze studie was de visuele uitkomst over het algemeen goed, met de uitzondering van necrotiserende en posterieure scleritis. De behandeling werd in oplopende zwaarte gegeven op basis van etiologie, ernst van de scleritis en de aanwezigheid van een onderliggende systemische ziekte. In totaal werden 47 patiënten behandeld met steroïdsparende medicatie. In de meeste gevallen betrof dit Methotrexaat (MTX), gevolgd door Mycofenolaat Mofetil (MMF). Bij 11 patiënten werd, na het falen van MTX of MMF, behandeling met TNF-alfa-remmers gestart. Globaal werd ongeveer bij de helft van de patiënten bij ieder steroidsparend middel behandelsucces bereikt. Hoewel Azathioprine hierop een uitzondering lijkt, omdat dit middel in onze studie niet effectief bleek bij patiënten met scleritis. In onze studie bleken necrotiserende scleritis, mannelijk geslacht, een langere duur van de symptomen bij presentatie, een onderliggende systemische ziekte en bilaterale scleritis indicatief voor een slechtere prognose. In multivariate analyse bleek het hebben van een bilaterale scleritis op enig moment tijdens het ziektebeloop de sterkste onafhankelijke voorspeller die geassocieerd was met een ernstiger ziektebeloop.

In **hoofdstuk 3** presenteren we de resultaten van onze studie bij 85 patiënten met serologisch bewezen syfilitische uveitis die behandeld werden in 5 verschillende tertiaire uveitis centra in Nederland. Uitkomstmaten van deze studie waren; visuele uitkomst, de effectiviteit van verschillende vormen van antibioticabehandeling en prognostische factoren. In deze studie bleek de algehele visuele prognose goed mits er tijdig adequate therapie werd gegeven. Alhoewel er bij 6 patiënten ernstig visueel verlies optrad door structurele

schade aan de oogzenuw en het netvlies. Verbetering van de gezichtsscherpte 6 maanden na start van de antibioticabehandeling werd gevonden in alle behandelingsmodaliteiten. Sommige niet-intraveneuze behandelgroepen waren klein qua aantal patiënten. Er werden geen statistisch significante verschillen gevonden in de gezichtsscherpte na 6 maanden follow-up in multivariabele analyse tussen de verschillende behandelmodaliteiten. Wel vertoonden de patiënten die werden behandeld met intraveneuze penicilline (hoewel niet statistisch significant) een tendens tot een betere gezichtsscherpte na 6 maanden follow-up. Er werden geen gunstige of nadelige effecten van extra orale steroïden of steroïde-injecties gevonden. Dit komt waarschijnlijk doordat corticosteroïden (oraal of per subconjunctivale injectie) aan de ernstigere gevallen waren toegediend. Voorspellende factoren werden geanalyseerd met betrekking tot de gezichtsscherpte na 6 maanden. In deze analyse waren een lage gezichtsscherpte bij presentatie en een vertraging in behandeling van meer dan 12 weken, allebei onafhankelijk geassocieerd met een minder gunstige visuele uitkomst na 6 maanden.

In **hoofdstuk 4** worden het diagnostisch proces, de klinische kenmerken en de uitkomst van 6 patiënten met een genetisch bevestigde retinale dystrofie, zich presenterend als intermediaire uveitis (IU) met cystoïd macula-oedeem (CME), uit 3 verschillende tertiaire uveitiscentra in Nederland gerapporteerd. Alle 6 patiënten presenteerden zich met een suboptimale gezichtsscherpte en IU met CME. De IU werd geclassificeerd als idiopathisch op basis van het uitsluiten van onderliggende verklarende oorzaken door reumatoloog of immunoloog. Bij presentatie of tijdens follow up werd bij geen van de 6 patiënten klinische tekenen van retinitis pigmentosa gevonden. Behandeling met immuun suppressie werd bij 5 patiënten gestart. Tijdens de follow-up werden bij gezichtsveldonderzoek verschillende mate van perifeer gezichtsveldverlies gevonden. Tijdens het beloop bleef, ondanks de behandeling, de CME aanhouden, nam het perifere gezichtsveldverlies toe en 3 patiënten rapporteerden in toenemende mate slechter zien in het donker. Bij alle patiënten werden elektroretinogrammen (ERG) verricht. Hierop werden verminderde scotopische en fotopische responsen gevonden. Daarnaast verminderde onder de systemische immuun suppressie de CME of ontsteking niet en bleef de gezichtsscherpte verlaagd. Het ziektebeloop en uitkomsten van aanvullende onderzoeken leidden tot de heroverweging van de diagnose en tot de verdenking op een retinale dystrofie. De diagnose van retinale dystrofie werd bij alle patiënten bevestigd door DNA-screening op bekende DNA-mutaties die verband houden met retinale dystrofieën. Een mutatie in het CRB1-gen werd gevonden bij 3 patiënten, 1 patiënt had een mutatie in het RP1-gen, 1 patiënt had een mutatie in het USH2A-gen en 1 patiënt had 2 dominante RD-genen. Gezien de resultaten bij deze 6 patiënten, zou retinale dystrofie moeten worden opgenomen in de differentiële diagnose van patiënten met therapieresistente, IU met CME op OCT. Het verdient aanbeveling in deze

patiëntengroep om bij de anamnese aandacht te hebben voor nachtblindheid en een eventuele familiegeschiedenis van retinale aandoeningen. Daarnaast draagt het onderzoek van het perifere gezichtsveld, het meten van het ERG en het tijdig betrekken van een oogarts met expertise op het gebied van retinale dystrofieën, bij aan het herkennen en diagnosticeren van een retinale dystrofie. Tijdige herkenning en dus vroege diagnose maakt adequate begeleiding mogelijk en voorkomt onnodige behandeling met immuun suppressie in deze patiëntengroep.

Hoofdstuk 5 is het eerste hoofdstuk van het tweede deel van dit proefschrift. In dit tweede deel worden de resultaten van de studies bij kinderen gerapporteerd. In hoofdstuk 5 wordt het onderzoek naar de vergelijking in effectiviteit van een hoge en lage dosering methotrexaat bij 42 kinderen met niet-infectieuze uveitis gepresenteerd. Uitkomstmaten zijn: tijd tot ziekteremissie met medicatie, steroïdsparend effect en bijwerkingen. Deze studie toont aan dat patiënten die worden behandeld met een hogere dosering MTX (≥ 15 mg/m^2/week) eerder ziekteremissie bereiken dan patiënten die worden behandeld met een lagere dosering MTX (<15 mg/m^2/week). Onze resultaten laten tevens zien dat een hogere dosering MTX (≥ 15 mg/m^2/week) toegediend via subcutane injectie het meest effectief is bij het bereiken van ziekteremissie met medicatie. De steekproefomvang bij de patiënten die worden behandeld met hogere dosering orale MTX is te klein om te interpreteren en om conclusies aan te verbinden. Metingen van de gezichtsscherpte na 6 en 12 maanden laten een beter resultaat zien in de groep die werd behandeld met hogere dosering MTX. Later in de follow-up is de visuele uitkomst tussen groepen met hoge en lage dosis vergelijkbaar. De hoog - en laag gedoseerde groepen zijn gelijk aan elkaar met betrekking tot de ernst van uveitis, incidentie van oculaire complicaties, de benodigde oogheelkundige chirurgische ingrepen, steroïdsparend vermogen van MTX, cumulatieve dosis MTX en gevonden bijwerkingen. Op basis van onze resultaten, het beste beschikbare bewijs uit de behandeling van reumatoïde artritis en onze eigen klinische ervaring, wordt een MTX-aanvangsdosis van ≥ 15 mg/m^2/week per subcutane toediening met een maximum van 25 mg/week aanbevolen voor de behandeling van niet-infectieuze uveitis bij kinderen. Na het bereiken van remissie kan een lagere (10-15 mg) - mogelijk orale - onderhoudsdosis worden overwogen om remissie te handhaven. Deze behandelingsstrategie leidt hopelijk tot kortere ziekteduur, preventie van visueel verlies en oculaire complicaties en tot rationeel gebruik van de verschillende behandelingsopties bij deze patiënten.

In hoofdstuk 6 presenteren we de resultaten van onze pilotstudie over fysieke fitheid, fysieke activiteit en psychosociale gezondheid bij 23 kinderen met uveitis. In totaal kwamen 42 patiënten in aanmerking voor het onderzoek, na exclusie van 1 patiënt, waren 23 patiënten bereid om deel te nemen aan het onderzoek. Deze 23 patiënten ondergingen algemeen lichamelijk - en oogheelkundig onderzoek. Daarnaast werden fysieke fitheid, fysieke activiteit, spierkracht en

gezondheid gerelateerde kwaliteit van leven (HR QoL) en vermoeidheid gemeten. Het gemiddelde gewicht en de Body Mass Index (BMI) van de kinderen met uveitis waren statistisch significant hoger in vergelijking met gezonde leeftijdsgenootjes. De 10 patiënten met juveniele idiopathische artritis (JIA)-gerelateerde uveitis hadden een statistisch significant hogere BMI dan de 13 patiënten met idiopathische uveitis. De fysieke fitheid werd gemeten aan de hand van het aeroob inspanningsvermogen en spierkracht. Het aeroob inspanningsvermogen was, hoewel net niet statistisch significant, lager dan de referentiewaarden van gezonde kinderen. De spierkracht was statistisch significant verminderd in onze groep patiënten in vergelijking met controles bij gezonde kinderen. Er werden geen verschillen in fysieke fitheid tussen JIA-gerelateerde en idiopathische uveitis gevonden. De kinderen met uveitis waren statistisch significant minder fysiek actief in vergelijking met gezonde leeftijdsgenoten en er werden geen verschillen gevonden tussen kinderen met JIA-uveitis en idiopathische uveitis. Voor de HR QoL en vermoeidheid werden vragenlijsten gebruikt die ingevuld werden door zowel ouder en kind. De kinderen zelf rapporteerden een normale HR QoL en vermoeidheid. Ouders rapporteerden over hun kinderen een statistisch significant lagere HR QoL en meer vermoeidheid in vergelijking met ouders van gezonde kinderen. Concluderend laten we in dit onderzoek zien dat patiënten met een niet-infectieuze uveitis risico lopen om vroeg in hun leven cardiovasculaire risicofactoren te ontwikkelen. Kinderen met uveitis hebben een hogere BMI, lagere fysieke fitheid en zijn minder fysiek actief in vergelijking met hun gezonde leeftijdsgenoten. Bovendien rapporteren ouders een lagere kwaliteit van leven en meer vermoeidheid over hun kinderen, vergeleken met de ouders van gezonde kinderen. Daarnaast vinden we geen verschillen tussen kinderen met idiopathische niet-infectieuze uveitis en kinderen met JIA-gerelateerde uveitis. Op basis van ons onderzoek is geen onderscheid te maken of de door ons gevonden effecten ontstaan door de systemische medicamenteuze behandeling, onderliggende ziekte of mogelijke systemische inflammatie bij uveitis. Het is belangrijk om bij de behandeling van uveitis op kinderleeftijd, naast de adequate oogheelkunde behandeling, aandacht te hebben voor de fysieke en psychosociale gezondheid en het risico op het ontwikkelen van cardiovasculaire risicofactoren in deze jonge patiëntengroep.

In **hoofdstuk 7** worden de resultaten van ons onderzoek naar de risicofactoren voor de ontwikkeling van medicamenteus oncontroleerbaar hoge oogdruk gerapporteerd. De studie werd uitgevoerd in een cohort van 196 kinderen met uveitis die behandeld werden in 2 tertiaire centra in Nederland. In 85 patiënten bleek glaucoomchirurgie nodig, de resterende 111 patiënten hadden op dat moment geen glaucoomchirurgie nodig en werden gebruikt als controlegroep. De chirurgiepatiënten waren bij eerste presentatie van de uveitis jonger (mediane leeftijd 6 versus 8 jaar, P = 0,008), hadden vaker uveitis anterior (78% versus 62%, P = 0,02) en vaker een JIA-gerelateerde uveitis (62% versus 35%, P

<0,001). De chirurgiepatiënten ondergingen vaker cataractchirurgie (80% versus 31%, P <0,001), hadden een hogere maximale intra-oculaire druk (IOP) (IOP 37 mmHg versus 27 mmHg, P <0,001) en gebruikten vaker meer dan 2 soorten glaucoommedicatie (83% versus 24%, P <0,001). Om mogelijke risicofactoren te identificeren, werden kenmerken die aanwezig waren bij presentatie opgenomen in een multivariabele Cox-survivalanalyse. Uit deze analyse bleek dat uveitis anterior en een hogere IOP bij presentatie onafhankelijk en significant geassocieerd waren met een hoger risico op glaucoomchirurgie. Daarnaast bleek dat 70% van de patiënten die meer dan 2 soorten glaucoommedicatie gebruikten glaucoomchirurgie nodig hadden binnen 1 jaar. Vroege verwijzing naar een glaucoomspecialist met ervaring in deze patiëntengroep kan bijdragen aan het tijdig herkennen van de noodzaak voor glaucoomchirurgie. Hierdoor kan glaucoomchirurgie vroeger in de ziekte plaatsvinden en onherstelbare schade voorkomen worden. Frequente controle bij kinderen met uveitis anterior, kinderen die met meer dan twee soorten glaucoommedicatie worden behandeld en kinderen met JIA- gerelateerde uveitis wordt daarom aanbevolen.

CURRICULUM VITAE

EDUCATION

Wietse Grieco Wieringa was born in Leens on the 26th of April 1972. After secondary school he started combining work and learning during his education to become an optician, optometrist and physician assistant ophthalmology. In 1995 he graduated as an optician (Hoofddorp), in 1999 he graduated as an optometrist (University of Applied Sciences, Utrecht), between 2004 and 2007 he followed modules of the MSc clinical optometry (City University, London) and in 2007 he started his training as a physician assistant (PA) ophthalmology at the University Medical Center Groningen, for which he graduated cum laude in 2010 (Hanze University of Applied Sciences, Groningen). In 2012 he got the opportunity to start his PhD project under supervision of Prof. Dr. J.M.M. Hooymans and Dr. L.I. Los while working at the outpatient ophthalmology departments of the UMC Groningen, OZG Delfzijl and Scheper Ziekenhuis Emmen.

WORK EXPERIENCE

From 1991 Wietse started his working career by working in a number of optics shops (Marree Optiek Assen, Cocon Oogmode Leeuwarden and Groningen), a refraction surgery clinic (Hanzevision Groningen), and several ophthalmology departments (UMC Groningen, OZG Delfzijl and Scheper Ziekenhuis Emmen). In 1999 and 2005 he got the opportunity to travel to Nouadhibou (Mauritania) to participate in an eye care project initiated by the foundation Help Mauritania. From 2007 and onwards he has been involved in educational and teaching activities for several professions in ophthalmology. From 2008 until 2014 he was a member of the optometry disciplinary court. After becoming a physician assistant ophthalmology in 2010, he founded in 2014 together with ophthalmic PA colleagues, the ophthalmology section of the Dutch PA association (NAPA), of which he is chairman since then. Currently, Wietse is working at the ophthalmology department of the University Medical Center Groningen as physician assistant and is involved in the ophthalmological care for patients with uveitis, glaucoma and macular disease.

LEISURE

In his spare time Wietse likes to read and practice endurance sports such as cycling, mountain biking and running. But he is basically interested in all sports from martial arts to table tennis. Next to work and leisure he is and has been socially involved in the boards of organizations that are committed to preserving cultural-historical heritage in the province of Groningen and in the village of Winsum (Gr).

Wietse is married to Gerda Brokelman, together they raise their three children; Lars (2003), Susan (2005) en Ewout (2007). They live – together with their dog and two cats - in Winsum (Gr).

DANKWOORD

Het afronden van dit proefschrift is gelukt dankzij de inspanning, kennis en ervaring van een grote groep mensen. Mijn naam is weliswaar verbonden aan dit boekje, maar het kan niet genoeg benadrukt worden dat zonder de hulp en ondersteuning van de hieronder genoemde personen dit proefschrift niet tot stand gekomen was.

Na het afronden van de opleiding tot physician assistant mondde het afstudeeronderzoek uit in een publicatie in Ophthalmology. Hieruit vloeide het promotietraject voort wat leidde tot dit proefschrift. Mogelijkheden, kansen en het kunnen benutten van beiden zijn onlosmakelijk verbonden met de mensen waar ik het vertrouwen van kreeg om deze stappen te maken. Daarom allereerst een woord van dank aan mijn promotoren, gevolgd door de mensen die gedurende mijn jaren in het AZG/UMCG een belangrijke rol gespeeld hebben in mijn loopbaan en ontwikkeling.

Prof. dr. Hooymans, beste Anneke. In 2002 was je als afdelingshoofd er mede voor verantwoordelijk dat ik werd aangenomen als optometrist op de afdeling oogheelkunde van het toenmalige AZG. Naderhand kreeg ik de kans om de opleiding tot physician assistant te volgen. De afronding van deze opleiding was min of meer de start van het promotietraject met jou als promotor. Jouw begeleiding, hulp bij het proefschrift, de altijd motiverende en inspirerende voortgangsgesprekken en het behouden van overzicht en vertrouwen op het bereiken van het einddoel hebben mij enorm geholpen. Veel dank hiervoor.

Dr. L.I. Los, beste Leonie. Als mijn dagelijkse begeleider hebben we de afgelopen jaren nauw samengewerkt in de kliniek en aan de diverse onderzoeksprojecten. Ik heb enorm veel van je geleerd. Jouw kennis, schrijfkwaliteiten, positief kritische grondhouding en hoge werktempo hebben zeer positief bijgedragen aan het tot stand komen van dit proefschrift. Je was (en bent) altijd benaderbaar voor vragen en overleg. Naast de vele gesprekken en overlegmomenten omtrent de lopende onderzoeken en patiëntenzorg was er eigenlijk altijd ruimte – ondanks de altijd drukke werkzaamheden – om te socializen. Dit laatste heeft ook zeer bijgedragen aan een prettige sfeer en goed werkklimaat. Als laatste wil ik je zeer bedanken voor de kans en het vertrouwen wat ik van je kreeg om als niet-dokter te promoveren.

Joke van Enk. Beste Joke. Jij hebt als manager zorg en bedrijfsvoering van de afdeling oogheelkunde een grote hand gehad in de taakherschikking en positionering van de vele ondersteunende beroepen in de oogheelkunde. Voor

mij persoonlijk heeft dat betekend dat er perspectief was en ik me verder kon ontwikkelen. Daarnaast ben je op een aantal belangrijke momenten opgekomen voor mijn belangen en heb je daarmee gezorgd voor rust, stabiliteit en continuïteit. Ik wil je bedanken voor het goede en constructieve contact door de jaren heen en de kansen en mogelijkheden die ik kreeg. Ik waardeer het bijzonder dat jij mijn promotie aanwezig bent.

Drs. B.A.E. van der Pol, beste Bert. Jij was als chef de clinique, oogarts en als opleider tijdens de physician assistant opleiding mijn eerste aanspreekpunt tijdens de dagelijkse gang van zaken. Ik heb veel aan je te danken. We hebben bijzondere en erg leuke dingen samen gedaan. Ik denk dan vooral terug aan Mauritanie, tal van onderwijsmomenten, congresbezoek en het vele samenwerken in de kliniek, Wat ik opgeschreven en gedeeld heb met je bij jouw afscheid in 2015 is onverminderd van kracht. Ik kijk met bijzonder goed gevoel terug op de lange periode van samenwerking en wil je danken voor je inzet, wijsheid, vertrouwen, kennis en humor.

Prof. Dr. N.M. Jansonius. Beste Nomdo, veel dank voor de ruimte en kansen die ik kreeg -ondanks de turbulente tijd waar we als ziekenhuis en afdeling soms zaten - om dit proefschrift tot een goed einde te brengen. Dank ook voor je scherpe blik, glasheldere analyses en zeer bruikbare adviezen in algemene zin en rondom het laatste hoofdstuk.

Prof. Dr. J. de Boer. Beste Joke, veel dank voor de fijne constructieve samenwerking, hulp en goede adviezen op meerdere momenten.

Een woord van dank aan de leden van de beoordelingscommissie. **Geachte Prof. dr. H. Bootsma, Prof. dr. A. Rothova en Prof. dr. N.M. Wulffraat.** Dank voor jullie bereidheid om plaats te nemen in de beoordelingscommissie en te opponeren. Ik heb het contact met jullie als prettig ervaren.

Drs. N.H. ten Dam – van Loon. Beste Ninette, het scleritisartikel kreeg mede zijn inhoud en omvang dankzij jouw bereidheid en hulp. Het contact door de jaren heen is bijzonder prettig en hartelijk. Ik ben je daar zeer erkentelijk voor.

Drs. J.G. Bollemeijer. Beste Jan Geert, dank voor de kans die ik kreeg om met je samen te werken aan het Luesartikel. Ik ben onder de indruk van je kennis en jouw bereidheid die te delen.

Charlotte van Meerwijk. Nadat jij betrokken raakte bij het glaucoomproject ging alles plots veel sneller en gemakkelijker. Dankzij jouw gedrevenheid, harde werken en vasthoudendheid is het gelukt om het 1e deel van het glaucoomproject toe te voegen aan dit proefschrift. Ik volg met belangstelling de verdere stappen

in jouw carrière. Dank dat je bij mijn kan promotie zijn en veel dank voor de fijne samenwerking, ik kijk uit naar het vervolg.

Lisette Hoeksema. Jij startte op het (toenmalige) LEO als onderzoekster toen ik daar nog zat als net afgestudeerde physician assistant en beginnend onderzoeker. We deelden veel ervaringen, schreven samen het uveitis onderzoeksprotocol, bezochten het IOIS congres (Valencia) en waren deelgenoot van bijzondere momenten in elkaars leven. Jij combineert een nuchtere constructieve kijk op zaken met een hoog werktempo en een mooi gevoel voor humor. Veel dank voor je luisterend oor, adviezen, vele gezellige momenten en de altijd bruikbare korting en bespaartips.

Bart Wullink. Samen zijn wij toch een beetje de LEO-veteranen geworden. Ik heb respect voor je onverwoestbare optimisme en relativeringsvermogen. Onze regelmatige gesprekken over ons enorme lijden in deze laatste afrondende fase hebben me er door getrokken. Veel dank voor je luisterend oor, wijze adviezen en humor. Binnenkort mag jij.

Drs. F. Hoogslag-Bienfait. Beste Francine, dank voor je altijd oprechte interesse in mijn proefschrift en je advies daarbij. Dank ook voor de fijne samenwerking binnen de uveitisgroep.

Dr. W. Armbrust. Beste Wineke, jij bent de drijvende kracht achter de samenwerking binnen ons ziekenhuis(en daar buiten) rondom de zorg voor kinderen met uveitis. Ik waardeer enorm de mogelijkheden die via en dankzij jou ontstonden en uitmonden in 2 hoofdstukken in dit proefschrift. Dank voor al je hulp, delen van kennis, adviezen, gezellige koffiemomenten en de echt heel erg leuke sportieve activiteiten waar ik via jou aan mee kon doen.

Dr. O.T.H.M. Lelieveld. Beste Otto, veel dank voor je bruikbare adviezen, delen van kennis en hulp rondom hoofdstuk 6.

Rosanne van Berkel. Beste Rosanne, veel dank voor al het door jouw verzette werk en de fijne samenwerking rondom hoofdstuk 6.

Secretariaat oogheelkunde; Diana, Ella, Fenna en Stella; Lieve dames van het secretariaat dank voor jullie hulp, luisterend oor en inzet.

(Oud) onderzoekers LEO (lab experimentele oogheelkunde). Ik ben ondertussen 1 van de langst zittende personen geweest op het LEO. Daardoor had ik het genoegen veel mensen te leren kennen en in meer of mindere mate met hen samen te werken. Daarom (niet in volgorde van voorkeur): Else, Michael, Kim, Sao Chung, Marielle, Esther, Francisco, Doety, Tim, Lisanne, Bernadette, Ronald ,

Danna, Christiaan, Margriet, Bart, Nancy, Marleen, Casper, Thom; dank voor alle hulp, gezelligheid en humor.

Stafleden van de afdeling oogheelkunde van het UMCG. Hartelijk dank voor de goede samenwerking, het in mij gestelde vertrouwen, interesse en aanmoedigingen door de jaren heen.

AOIS afdeling oogheelkunde UMCG; dank voor de fijne samenwerking in de kliniek, de goede sfeer, samenwerking en de met regelmaat getoonde interesse in mijn proefschrift

Dagelijks bestuur, management en coördinatoren polikliniek oogheelkunde UMCG; Beste Janneke, Richard, Rogier en Ruben. Veel dank voor jullie hulp, flexibiliteit en creativiteit wanneer ik weer eens aanklopte met een verzoek.

Leden van het multidisciplinair (MDO-uveitis) uveitis team. Beste Elizabeth, Ina, Janny, Wineke en Bram. Dank voor de goede samenwerking en jullie interesse in mijn vorderingen qua onderzoek.

MMA afdeling oogheelkunde UMCG. Dank voor jullie ondersteuning en hulp. In het bijzonder een woord van dank aan **Chantal.** Veel dank voor jouw hulp rondom opzoeken en zorgvuldig bewaren van allerlei gegevens.

P**aramedici (TOA, orthoptisten, optometristen, verpleegkundigen en polikliniekassistenten) afdeling oogheelkunde UMCG.** Dank voor jullie interesse in de diverse onderzoeksprojecten en fijne samenwerking door de jaren heen

Een woord van dank aan de mede auteurs van de diverse artikelen. **Dr. Y Hettinga, beste Ymkje** dank voor het beschikbaar stellen en de samenwerking rondom hoofdstuk 4. **Drs. E. Legger, beste Elizabeth** dank voor je bijdrage aan hoofdstuk 5. **Drs. O.A.R. Misotten en Dr. I. Meenken** dank voor jullie bedragen aan hoofdstuk 3.

Collega's oogheelkunde UMC Utrecht. Beste Anne-Mieke, Fleurieke en Kamil, dank voor jullie hulp en gastvrijheid.

Wim Berghuis. Beste Wim, hoewel je niet meer werkt op de afdeling oogheelkunde wil ik je danken voor je financieel inzicht en bruikbare adviezen.

NAPA vakgroepbestuursleden oogheelkunde; Beste Chantal, Gerlineke, Dave, Rini en Hilke, wat hebben we samen ondertussen veel bereikt! Het samenwerken met jullie is bijzonder prettig en geeft energie. Veel dank voor jullie belangstelling en aanmoedigingen door de jaren heen.

Het selecte groepje leden van The Pink Panthers Cycling team. Beste Hero, Ruben en Peter, veel dank voor jullie vriendschap, het delen van lief en leed en de tal van mooie tochten die we samen reden. Ik hoop dat we dit vaak samen kunnen blijven doen en kijk uit naar de komende rit in de Pyreneeën.

Mijn goede vrienden Erik, Jan-Willem, Pieter en Wolter. Ik voel me rijk met vrienden zoals jullie. Ik waardeer het bijzonder dat jullie bij mijn promotie aanwezig zijn en ik dank jullie voor de lange vriendschap en loyaliteit in tijden van minder contact door drukke levensfasen.

Mijn lieve schoonfamilie. Ik voel me enorm thuis bij jullie en geniet van de vele gezellige en leuke, feestjes, vakanties en uitstapjes. Veel dank voor alle hulp, belangstelling en support. Jullie zijn echt en jullie zijn er ook echt voor elkaar. Niet alleen als alles crescendo gaat maar vooral ook als het leven soms onvermijdelijk tegen zit.

Mijn moeder. Lieve mam, dank voor je onvoorwaardelijke steun en liefde. Ik vind het knap van je hoe je de draad weer opgepakt hebt na een moeilijk jaar met grote veranderingen.

Mijn broer. Beste Jaap, dank voor je hulp en adviezen rondom hoofdstuk 2 (en echt mooi dat dit resulteerde in een 2e auteurschap) en op een aantal andere belangrijke momenten. Ik ben oprecht blij dat jij paranimf bent op deze voor mij memorabele dag. Het afgelopen decennium was voor ons beiden - naast werk en privé - een periode van veel verhuizingen en mantelzorg. Ik hoop dat de toekomst rustiger wordt met meer tijd & ruimte voor normalere en leukere gezamenlijke activiteiten.

Mijn zus. Lieve Florieke. Ondanks de onzekerheid en onrust in jouw thuissituatie, maak je tijd voor onze gezamenlijke taak er te zijn voor de ouderen in onze familie. Ik waardeer dat enorm en hoop dat er daarnaast ruimte is voor het ondernemen van leuke activiteiten met elkaar. Veel dank voor de oprechte gesprekken, je luisterend oor en bruikbare adviezen met name in de laatste periode. Ik ben heel blij en trots dat jij mij terzijde staat als paranimf.

Als laatste het thuisfront; Lieve Lars, Susan en Ewout. Ik ben zo enorm blij met en trots op jullie. Wat doen jullie het goed! Ik kijk uit naar jullie verdere stappen en ontwikkeling. Een belangrijk deel van mijn inspiratie en motivatie ontstaat dankzij jullie. Bedankt om wie jullie zijn, ik hou van jullie!

De slotwoorden van dit dankwoord kunnen maar voor één persoon zijn; **lieve Gerda**, dank voor je onvoorwaardelijke liefde, steun en wijze raad. Ik hou van je, jij bent mijn thuis, waar we ook zijn.

LIST OF ABBREVIATIONS

AGD = age and gender dependent
ANA = antinuclear antibody
ANCA = antineutrophil cytoplasmic antibody
AqH = aqueous humor
AZA = azathioprine
BMI = body mass index
CSF = cerebrospinal fluid
CHAQ = child Health assessment questionnaire
CI = confidence interval
CIA = chemiluminescence immunoassay
CME = cystoid macular edema
CO_2 = carbon dioxide
CsA = cyclosporine
CTX = cyclophosphamide
DI = disability index
DNA = Deoxyribonucleic acid
EIA = enzyme immunoassay
ERG = electroretinogram
FA = fluorescein angiography
FTA-ABS = Fluorescent treponemal antibody absorption test
FU = follow up
GI = gastro intestinal
HAART = highly active antiretroviral therapy
HHD = hand-held dynamometry
HIV = human immunodeficiency virus
HLA = human leukocyte antigen
HR = Hazard ratio
HRmax = peak heart rate
HR-QoL = health related quality of life
IM = Intra muscular
IOP = intraocular pressure
IQR = inter quartile range
ISCEV = International Society for Clinical Electrophysiology of Vision
IU = Intermediate uveitis
IUSTI = international union against sexually transmitted infections
IV = intravenous
JIA = juvenile idiopathic arthritis
Kg = kilogram
LogMAR = logarithm of the minimum angle of resolution

LPA = light physical activity
MAR = missing at random
MMF = mycophenolate mofetil
MRC = Medical research council
MTX = methotrexate
MVPA = moderate-to-vigorous physical activity
NLP = no light perception
NSAIDs = nonsteroidal anti-inflammatory drugs
OCT = optical coherence tomography
OID = ocular inflammatory disease
PA = physical activity
PCR = Polymerase chain reaction
PedsQL = pediatric quality of life inventory
PGA = physician global assessment
QoL = quality of life
RA = rheumatoid arthritis
RD = Retinal dystrophies
RPR = Rapid Plasma Reagin
SC = sub cutaneous
SD = standard deviation
SPSS = statistical package for the social sciences
STI = sexually transmitted infection
SUN = Standardization of uveitis nomenclature
TNF - α = tumor necrosis factor - α
TPHA = Treponema pallidum haemagglutination assay
TPPA = Treponema pallidum particle agglutination assay
UMCG = university medical center of Groningen
UMCU = university medical center of Utrecht
US = ultrasonography
VA = visual acuity
VDRL = Venereal Disease Research Laboratory
VF = Visual field
VO_2peak = peak oxygen consumption
WHO = World Health Organization
W_{peak} = peak work rate