Uveitis in Childhood • Complications and Treatment with Emphasis on Juvenile Idiopathic Arthritis • Karen M. Sijssens • 2008

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Uveitis in Childhood

Complications and Treatment with Emphasis on Juvenile Idiopathic Arthritis

Uveitis bij Kinderen
Complicaties en Behandeling met de Nadruk op Juveniele Idiopathische Artritis
(met een samenvatting in het Nederlands)

Proefschrift

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Karen Maria Sijssens

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Voor Joeri, Job en mijn ouders

Contents

Chapter 1

Introduction

THE AIM OF THIS THESIS is primarily to investigate the development of complications in uveitis in childhood and to evaluate the treatment options for the most visual threatening conditions with emphasis on juvenile idiopathic arthritis (JIA)-associated uveitis. A second aim is to analyze which immune mediators in the aqueous humor are involved in the pathogenesis of pediatric uveitis.

Introduction

Uveitis is a potentially blinding disease and is responsible for about 10% of the visual handicap in the Western world and 10%-20% of all blindness in the United States.[1;2] In a Dutch study, 17% of children with uveitis developed unilateral legal blindness and 2% developed bilateral legal blindness with macular scars and secondary glaucoma as the major causes.[3] In the case of JIA-associated uveitis sever visual loss (less than 20/200) was found in almost one third of the eyes in a study of 1996 and with an incidence of 23% (14/60 eyes) in a study of 2007.[4;5]
The poor visual prognosis of pediatric uveitis inspired us to investigate the ocular complications of uveitis in childhood.

Uveitis in children versus adults

Uveitis in childhood differs in various clinical aspects from uveitis in adulthood.
First, the association with systemic diseases is different in children. JIA is the most common systemic association in children.[6] In adults sarcoidosis is a common cause of uveitis, which is rarely the underlying cause of the intraocular inflammation in children.[6]
Second, uveitis in childhood is frequently asymptomatic, especially in case of association with JIA.[7]
A third difference is that even though a diminished visual acuity is present, most children will not complain. Therefore, uveitis in childhood is frequently detected during routine screening examination for visual acuity or after strabismus has developed. These cases might already have ocular complications at the first visit to the ophthalmologist.
Fourth, ophthalmologic examination in very young children might be difficult. Therefore, a good relationship between child, parents and physician is necessary for a correct ophthalmologic investigation. An uncooperative or moving patient can make the slit-lamp examination very challenging. Occasionally, ophthalmologic examination under general anesthesia is necessary especially for measuring the intraocular pressure.
Fifth, in the case of systemic treatment, one should consider the effect on growth and skeletal development. Treatment with corticosteroids may delay the pubertal growth and might result in a lower peak bone mass leading to premature osteoporosis and its complications.[8]
Sixth, ocular surgery in children is generally more complicated due to anatomical and functional characteristics typical of this age, which include the small globe size; increased tissue reactivity; lower scleral rigidity and changing axial length.[6;9;10]

Finally, in young children, there is the risk of developing amblyopia due to ocular complications or long-term treatment with mydriatics.
All the above-mentioned differences between children and adults lead to the conclusion that children with uveitis need a specific treatment strategy.

Epidemiology

In the Western world the annual incidence of uveitis is between 17 and 52 per 100 000 population and the prevalence is 38 to 714 cases per 100 000 population.[11] In children (age 16 years or less) however, uveitis is less frequently seen than one should expect from the age structure of the population (5%-10% instead of 20% of the total uveitis population).[12-15] In North America and in Europe the annual incidence of childhood uveitis is 4.3 to 6.9 per 100 000 and the prevalence is about 30 cases per 100 000.[16]

Classification of uveitis

Uveitis can be classified according to anatomic localization, underlying cause, type of inflammation (granulomatous and non-granulomatous), severity and clinical course of inflammation (acute or chronic) and uni- or bilaterality. The anatomic classification of uveitis according to the standardization of uveitis nomenclature (SUN) working group is anterior uveitis (primary site of inflammation: anterior chamber), intermediate uveitis (primary site of inflammation: vitreous), posterior uveitis (primary site of inflammation: retina or choroid) and panuveitis (primary site of inflammation: anterior chamber, vitreous, retina or choroid).[17;18] Anterior uveitis is the most common anatomical category found in children (30.4% - 56.9%).[3;16;19;20]

Etiology

The etiology of uveitis in childhood is very diverse and in many children (21.5% - 52%) the underlying cause is unknown (Table 1).[3;5;16;20-24] In general, the etiologic backgrounds of uveitis in childhood are similar to that in adults with the exception of the systemic underlying causes. JIA is the most frequent associated systemic disease and is responsible for about 40% of all cases of childhood uveitis and of 80% of all children with anterior uveitis.[5;21;25]

Table 1. Etiology of uveitis in childhood

Infectious	Congenital	Toxoplasmosis (Toxoplasma gondii) Rubella virus Cytomegalovirus Herpes Simplex virus Syphilis (Treponema pallidum)
	Acquired	Toxoplasmosis (Toxoplasma gondii) Toxocariasis (Toxocara canis) Varicella Zoster virus Herpes Simplex virus Lyme disease (Borrelia burgdorferi) Tuberculosis (Mycobacterium tuberculosis) Fungal disease Whipple's disease (Tropheryma whippelii) Leprosy (Mycobacterium leprae) Cat scratch disease (Bartonella henselae)
Non-infectious	Systemic	Juvenile idiopathic arthritis (JIA) Sarcoidosis Behçet's disease Psoriasis Inflammatory bowel disease Tubulointerstitial nephritis and uveitis syndrome (TINU) Systemic lupus erythematosus (SLE) Multiple sclerosis (MS) Vogt-Koyanagi-Harada syndrome (VKH) Kawasaki disease Wegener's granulomatosis Chronic infantile neurologic cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome (CINCA/NOMID) Blau syndrome Cogan syndrome
	Specific ocular diseases	Pars planitis Fuchs' heterochromic uveitis (Rubella virus-associated) Sympathetic ophthalmia Retinal vasculitis Diffuse unilateral sclerosing neuroretinitis (DUSN) Neuromyelitis optica/Devic's syndrome Acute multifocal posterior placoid pigment epitheliopathy (AMPPE) Traumatic uveitis
	Toxic	Drug-indiced (rifabutin)
Masquerade	Neoplastic	Retinoblastoma Leukemia Juvenile xanthogranuloma Posttransplantation lymphoproliferative disease (PTLD)
	Non-neoplastic	Intraocular foreign body Retinal detachment
Idiopathic		

JIA-associated uveitis

In 1910, Ohm was the first to report a case of band keratopathy in a child with arthritis.[26] However, it was not until 1941 that the relationship between childhood arthritis and iridocyclitis was established by Blegvad.[27]

JIA is one of the most common autoimmune diseases of childhood, with a prevalence of 100 per 100 000 and annual incidence of 10 to 20 per 100 000 children.[28] The general definition of JIA is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks whereby other known conditions, such as for example sarcoidosis or tuberculosis are excluded.[29] JIA is subdivided into 7 subgroups according to the International League of Associations for Rheumatology (ILAR) criteria (Table 2).[29] Eye inflammation occurs in about 12% of all children with JIA.[30] However, the percentages of uveitis per subgroup are diverse with the highest risk of uveitis in patients with oligoarthritis (persistent and extended, 10-30%) and the lowest in children with systemic arthritis (Table 2).[30;31] JIA-associated uveitis is a chronic, mostly bilateral anterior uveitis which is usually asymptomatic with an insidious onset, with the exception in enthesitis-related arthritis and rarely in psoriatic arthritis where the uveitis might be acute.

Table 2. Uveitis in juvenile idiopathic arthritis classified according to International League of Associations for Rheumatology criteria

Juvenile idiopathic arthritis classification according to International League of Associations for Rheumatology criteria[a]		Uveitis OR (95% CI)[b]
Systemic arthritis	≥1 joints affected	1
Oligoarthritis		
Persistent	1-4 joints affected	19 (4.7 – 78.1)
Extended	>4 joints affected after the first 6 months	33 (7.9-136.6)
Polyarthritis (rheumatoid factor negative)	≥5 joints affected	5 (1.1-20.9)
Polyarthritis (rheumatoid factor positive)	≥5 joints affected	3 (0.4-21.8)
Psoriatic arthritis		11 (2.7-48.3)
Enthesitis-related arthritis		7 (1.7-30.3)
Other arthritis		12 (2.9-52.4)

OR (95% CI)=Odds ratio (95% confidence interval).

[a]Petty RE, Southwood TR, Manners P, *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.

[b]Heiligenhaus A, Niewerth M, Ganser G, *et al.* Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford) 2007;46:1015-9.

In eyes with moderate to severe uveitis, cells can be seen in the anterior vitreous and the inflammation may also spread to the posterior parts of the eye, sometimes resulting in cystoid macular edema.[32]
Chronic anterior uveitis in combination with arthritis is also associated with sarcoidosis and the rare chronic infantile neurologic cutaneous and articular/ neonatal onset multisystem inflammatory disease (CINCA/NOMID) syndrome. The main difference between JIA-associated and sarcoidosis-associated uveitis is that in the case of sarcoidosis iris nodules and posterior segment manifestations (chorioidal granuloma, vasculitis and peripheral multifocal choroiditis) occur, the latter of which are seen in 14-43%.[33] In CINCA/NOMID syndrome the uveitis is usually mild without posterior synechiae, glaucoma and cataract development.[34] However, in 83% of patients with CINCA/NOMID syndrome, optic disc abnormalities were seen whereas these are only seen in 6% of the patients with JIA-associated uveitis.[3;34]
Risk factors for the development of uveitis in JIA patients include: gender (female:male = 2:1), pattern of initial joint disease; young age (<6 years) at onset of arthritis; duration of arthritis <4 years; positive antinuclear antibodies (ANA) and possibly the presence of HLA-DRB1*11.[8;35-37] The presence of HLA-DRB1*08 might be protective for the development of uveitis.[37] It is still a matter of controversy whether boys and ANA-negative patients develop more ocular complications or not.[36;38] Furthermore, the presence of elevated serum levels of α2-globulin at the time of diagnosis of arthritis and a short time interval between arthritis onset and the first appearance of uveitis is associated with a severe uveitis course in children with oligoarticular JIA.[39]

Screening of children with JIA

Because the intraocular inflammation is usually asymptomatic, screening for uveitis is essential for improving the visual outcome of these children. The ophthalmologic screening of children with JIA is essential for early diagnosis and the immediate start of treatment of the intraocular inflammation at the time of diagnosis, since the presence of ocular complications at the first ophthalmologic examination is associated with a worse visual outcome.[36;40] Screening protocols for uveitis have been developed in the screening diagram of the American Academy of Pediatrics (Table 3).[41] Other screenings protocols have been postulated by Southwood and Ryder and more recently by the suggested guidelines for screening of Heiligenhaus (Table 4), which follows the classification of the International League of Associations for Rheumatology (ILAR) criteria.[30;42]

Table 3. Guidelines for ophthalmologic screening for uveitis in children with juvenile idiopathic arthritis according to the American Academy of Pediatrics

	Age of Onset	
JIA subtype at onset	**< 7 year[a]**	**≥ 7 year[b]**
Oligoarhritis		
ANA-positive	High risk: every 3-4 months[c]	Medium risk: every 6 months
ANA-negative	Medium risk: every 6 months	Medium risk: every 6 months
Polyarthritis		
ANA-positive	High risk: every 3-4 months[c]	Medium risk: every 6 months
ANA-negative	Medium risk: every 6 months	Medium risk: every 6 months
Systemic arthritis	Low risk: every 12 months	Low risk: every 12 months

ANA=antinuclear antibody test; JIA=juvenile idiopathic arthritis.
[a] All patients are considered at low risk 7 years after the onset of arthritis and should have yearly ophthalmologic examinations indefinitely.
[b] All patients are considered at low risk 4 years after the onset of arthritis and should have yearly ophthalmologic examinations indefinitely.
[c] All high-risk patients are considered at medium risk 4 years after the onset of their arthritis.

Pathogenesis of JIA-associated uveitis

The exact pathogenesis of the intraocular inflammation in children with JIA is not known. It is generally regarded that T-cell-dependent immunological events play a crucial roll in the pathogenesis of uveitis.[43] Recently, a case of a hypotonic enucleated eye of a child with JIA-associated uveitis was reported in which immunohistochemical findings demonstrated predominantly infiltrating B-cells.[44] However, this observation was made in the end stage of JIA-associated uveitis and till now it is not known which are the primary infiltrating cells in the eye at the onset of uveitis.

Treatment of JIA-associated uveitis

The aim of treatment of JIA-associated uveitis is the complete elimination of all active inflammation in the eye at all times, to prevent or minimize the development of complications. Difficulties in the treatment of children are the possible poor compliance and the development of side-effects of the systemic treatment. Close cooperation with the pediatric rheumatologist is necessary for choosing treatment to benefit both arthritis and uveitis and for monitoring for possible side-effects of the treatment.

The initial management of the intraocular inflammation consists of topical corti-

Table 4. Recommended screening intervals for uveitis in patients with juvenile idiopathic arthritis as classified by International League of Associations for Rheumatology criteria by Heiligenhaus *et al*

JIA subgroup	ANA	Age at JIA onset (years)	JIA duration (years)	Recommended screening intervals (months)
Oligoarthritis Polyarthritis RF- Psoriatic arthritis Undifferentiated arthritis	Positive	≤6	≤4	3
			>4	6
			≥7	12
		>6	≤2	6
			>2	12
	Negative	≤6	≤4	6
			>4	12
		>6	NA	12
Enthesitis-related arthritis Polyarthritis RF+ Systemic arthritis	NA	NA	NA	12
Patients with uveitis	NA	NA	NA	According to uveitis course

ANA=antinuclear antibodies; JIA=juvenile idiopathic arthritis; NA=not applicable, RF=rheumatoid factor.

costeroid therapy, mydriatics and cycloplegics. To minimize the risk of amblyopia, short-acting mydriatics can be used during the night. In the case of refractory uveitis, treatment with periocular corticosteroid injections (if necessary under general anesthesia) or oral corticosteroids may be used. The use of long-term systemic corticosteroids should be avoided because of adverse effects (inhibition of linear growth). If the response of uveitis to topical corticosteroids is insufficient, treatment with immunosuppressive drugs should be initiated. The choice of immunosuppressive drugs consists of antimetabolites (azathioprine, methotrexate, mycophenolate mofetil and leflunomide), T-cell inhibitors (cyclosporine and tacrolimus) and alkylating agents (cyclophosphamide and chlorambucil).[45] Methotrexate is the most common immunosuppressive agent used in children, especially in JIA. It is generally safe, well tolerated, easily administrated and does not affect future reproductive potential.[46] Alkylating agents have the potential for serious long-term side effects and therefore their use is limited for uveitis. Other alternatives for the treatment of JIA-associated uveitis are biologics. Biologics used for the treatment of JIA-associated uveitis are infliximab, adalimumab and anakinra.[47] The first 2 biologics are tumor necrosis

factor (TNF) inhibitors which bind to both soluble and transmembrane forms of TNF-α.[48;49] The third, anakinra, is an interleukin-1 receptor antagonist and is an alternative biological agent for children with JIA in whom the intraocular inflammation is resistant to anti-TNF therapy.[47] Etanercept is a TNF inhibitor which binds solely to the transmembrane form of TNF-α and has been shown to be less effective for the treatment of JIA-associated uveitis.[48;49] In future, there might be a role for other biologics such as daclizumab, interferon α-2 and rituximab.

Complications of JIA-associated uveitis and their treatment options

Hypotony and phthisis are the most feared irreversible complications of JIA-associated uveitis which occur in about 4-17% (Figure 1).[24] Other complications are posterior synechiae (35-70%, Figure 2), cataract (35-65%), band keratopathy (25-55%, Figure 3-4), secondary glaucoma (10-42%) and macular edema (7-42%).[24] The presence of posterior synechiae at the time of diagnosis of uveitis is associated with an increased risk of the development of complications such as cataract and glaucoma.[36] Band keratopathy is an accumulation of calcium within the corneal epithelium and at the level of Bowmans' membrane often beginning at the limbus at 3 o'clock and 9 o'clock and caused by longstanding intraocular inflammation.[50] When band keratopathy is affecting the visual acuity or causing ocular irritation, chelation of the cornea with ethylene diamine tetra-acetic acid (EDTA) can be performed.[51] Cataract in uveitis eyes develops for several reasons. Anterior subcapsular lens opacities are the result of the intraocular inflammation in the anterior chamber or the presence of posterior synechiae between iris and lens. Posterior subcapsular cataract might result from local or systemic treatment with corticosteroids.[9;10;46] The implantation of an intraocular lens has been a subject of controversy, since serious complications such as hypotony, cyclitic or fibrous membrane formation and macular edema may develop.[52;53] In some reported cases the intraocular lens had to be removed due to cocoon formation, intractable uveitis or other serious complications.[54]

Elevation of the intraocular pressure is mostly the result of blockage of the aqueous outflow due to inflammation of the trabecular meshwork and/or peripheral anterior synechiae and pupillary block due to posterior synechiae and secondary angle closure.[32] It is known that the sudden rise of intraocular pressure might occur when the uveitis is brought under control with topical corticosteroids or immunosuppression.[55] If the intraocular pressure is elevated in children, progression to secondary glaucoma with cupping of the optic disk and visual field loss can develop very quickly (Figure 5).[6] Carbonic anhydrase inhibitors are the first choice of topical therapy for secondary glaucoma followed by beta blockers and alpha-2

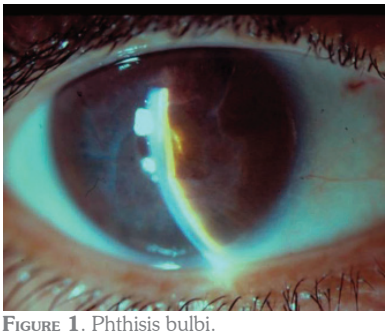

Figure 1. Phthisis bulbi.

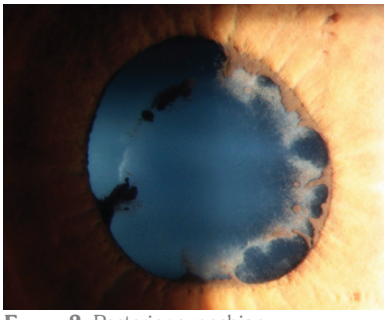

Figure 2. Posterior synechiae.

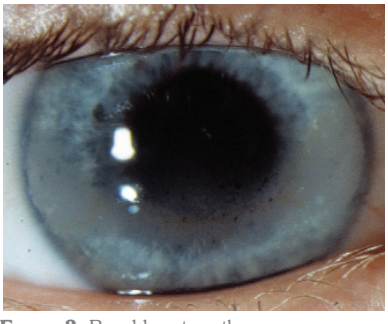

Figure 3. Band keratopathy.

Figure 4. Advanced band keratopathy and cataract.

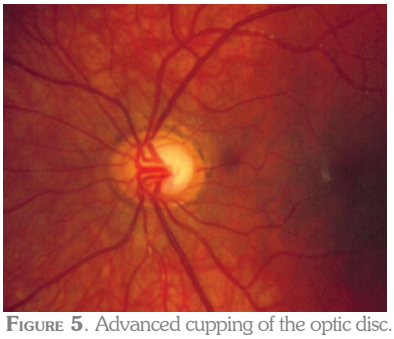

Figure 5. Advanced cupping of the optic disc.

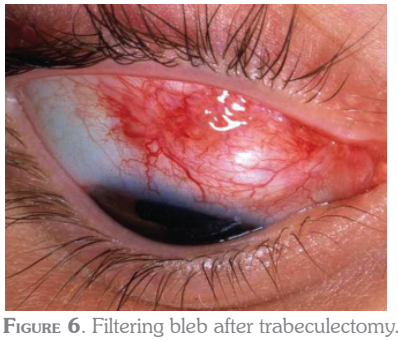

Figure 6. Filtering bleb after trabeculectomy.

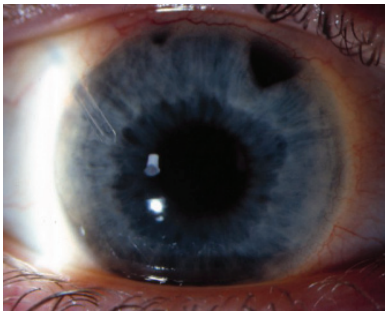

Figure 7. Tube of glaucoma drainage implant in the anterior chamber at 10 o'clock with a previously performed trabeculectomy at 1 o'clock in the right eye.

agonists.[56] Foster *et al.* found that intraocular pressure could be controlled with topical medications in 17% (7/41) and with topical medications plus oral carbonic anhydrase inhibitor in 37% (15/41) of patients with JIA-associated uveitis.[55] Surgical techniques for the management of secondary glaucoma in childhood uveitis consist of trabeculectomy with intraoperative application of mitomycin-C (Figure 6), goniotomy and the implantation of drainage devices (Figure 7).[46] However, there is no consensus about which surgical procedure should be performed in a specific situation. Even though the glaucoma surgery is successful, still additional topical anti-glaucoma medication is necessary to control the intraocular pressure in a high proportion of patients .[46]

For all surgical interventions in children with (JIA-associated) uveitis it is essential that the uveitis is in remission with medication. Therefore it is advisable to attempt to control the intraocular inflammation for a minimum of 3 months before surgery if the ocular condition allows it.[46;57]

Finally, if the chronic anterior uveitis in JIA spreads to the posterior part of the eye, it can cause vitritis and in severe cases cystoïd macular edema or disc edema.[32] In severe uveitis with epiretinal membranes, retinal detachment, and finally hypotony and phthisis bulbi may occur. Hypotony might be the result of traction on the ciliary body by ciliary membranes leading to its detachment or of ciliary body atrophy due to longstanding JIA-associated uveitis.[46]

To pursue the aim of this thesis, we tried to answer the following questions:

1. Which children with uveitis are at risk of developing secondary glaucoma?
2. Which surgical procedure for secondary glaucoma is most successful in children with JIA-associated uveitis?
3. What are the risk factors for the development of cataract in JIA-associated uveitis?
4. Is the implantation of an intraocular lens associated with more long-term ocular complications in children with JIA-associated uveitis?
5. Which cytokines in the *eye* are involved in the pathogenesis of uveitis in childhood?

Outline of the thesis

In **chapter 1** we give a general overview of uveitis in childhood with emphasis on JIA-associated uveitis.
In **chapter 2** we investigate which children with uveitis are at greatest risk of developing ocular hypertension and secondary glaucoma, by performing a retrospective analysis on 147 consecutive children with uveitis.
In **chapter 3** we compare the surgical treatment of secondary glaucoma by trabeculectomy (27 eyes) or by the implantation of an Ahmed glaucoma valve (13 eyes) in children with JIA-associated uveitis to evaluate which technique is most successful.
In **chapter 4** we address the question of which factors accelerate the development of cataract requiring surgery in JIA-associated uveitis, by performing a retrospective analysis of 53 children with JIA-associated uveitis.
In **chapter 5** we describe the long-term complications and visual acuity of 19 aphakic and 29 pseudophakic eyes of children with JIA-associated uveitis and of 17 pseudophakic eyes of children with uveitis not associated with JIA to determine whether intraocular lens implantation is a risk factor.
In **chapter 6** we analyze 16 immune mediators in the aqueous humor of 25 children with uveitis and 6 children without uveitis in order to identify the factors that mediate the immune response in the eye.
In **chapter 7** we compare the immune mediator profile in the aqueous humor of 12 children, 16 adolescents and 35 adults with uveitis to determine the immune mediator profile in the eye in relation to age.
In **chapter 8** we report a case of an unusual combination of symptoms, specifically keratitis and multiple subepithelial round corneal nebulae in combination with uveitis and arthritis in a preschool girl who was later on diagnosed with sarcoidosis.
In **chapter 9** we report a case of presumed Fuchs heterochromic uveitis in a boy who had not been vaccinated against rubella.
The English and Dutch summary, conclusions and considerations form **chapter 10**.

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Chapter 2

Ocular hypertension and secondary glaucoma in children with uveitis

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Abstract

Purpose: To identify the risk factors for ocular hypertension and secondary glaucoma in children with uveitis.

Design: Retrospective observational case series of 147 patient records.

Participants: Two hundred fifty-six eyes of 147 children with uveitis diagnosed before the age of 16 years.

Methods: Data were obtained from the medical records of children with uveitis evaluated at our institute from 1990 through 2004.

Main Outcome Measures: Localization and course of uveitis (acute or chronic), underlying systemic disease, onset of ocular hypertension, onset of secondary glaucoma, treatment with corticosteroids, antinuclear antibodies (ANAs), lens extractions, number of blind eyes at onset and during follow-up, and the duration of follow-up.

Results: Elevated intraocular pressure developed in 35% of children with pediatric uveitis regardless of the form or type of uveitis during a follow-up of 5 years. Secondary glaucoma, however, developed more frequently in juvenile idiopathic arthritis-associated uveitis (38%) compared with other forms of uveitis (11%) and more frequently in children with uveitis who were ANA positive (42%) than in those who were ANA negative (6%). Elevated intraocular pressure occurred in two thirds of all children within the first 2 years after the diagnosis of uveitis. Except for patients with juvenile idiopathic arthritis-associated uveitis, periocular corticosteroid injections represented an additional risk factor for secondary glaucoma, but this risk was limited to the early phase of the disease process.

Conclusions: In children with uveitis in this series, juvenile idiopathic arthritis-associated uveitis and ANA-positive uveitis without evidence of arthritis are the most important risk factors for developing secondary glaucoma.

Introduction

Secondary glaucoma (SG) is a frequent complication of uveitis and a major cause of visual loss in children with uveitis.[1] Kanski and Shun-Shin reported that one third of the glaucomatous eyes of children with uveitis resulted in no light perception.[2] There are several explanations for this poor prognosis, such as a late detection as a result of uncooperative patients, lack of response to conventional glaucoma treatment, and poor results of conventional glaucoma surgery.[3] In the general uveitis population, SG is most frequently associated with chronic granulomatous anterior uveitis of unknown origin or with uveitis associated with sarcoidosis and juvenile idiopathic arthritis (JIA).[4] Because the visual prognosis of SG in children is poor, prevention, early detection, or both may improve the visual prognosis in this population. The purpose of our study was to investigate which children with uveitis are at increased risk of experiencing elevated intraocular pressure (ocular hypertension, SG, or both), particularly combined with poor visual outcome. Special attention was paid to anatomic type and causes of uveitis, associated systemic diseases, various treatment methods, and previous cataract surgery.

Materials and methods

We reviewed the medical records of 173 children with uveitis. These children were identified in a complete database search of the FC Donders Institute of Ophthalmology, University Medical Center, Utrecht, the Netherlands, from 1990 up to and including 2004. Only those patients with onset of ocular inflammation before the age of 16 years and follow-up of at least 6 months were included in this study. Our center combines a secondary and a tertiary referral function. Children were referred by the ophthalmologists of secondary referral hospitals or by the pediatric rheumatologists of our medical center. The pediatric rheumatologists referred children for uveitis screening according to the criteria of the American Academy of Pediatrics in cases of JIA or other systemic diseases.[5] We recorded the following clinical data for each patient: gender, race, family history of glaucoma, age at onset of uveitis, localization and course of uveitis (acute or chronic), laterality, underlying systemic disease, antinuclear antibody (ANA) status, onset of ocular hypertension (OHT), onset of SG, treatment with periocular or systemic corticosteroids, cataract surgery, number of blind eyes at onset and during follow-up, and the duration of follow-up.

Diagnosis of uveitis was based on the criteria of the International Uveitis Study Group.[6] The uveitis was considered chronic if the duration of active ocular

inflammation was longer than 3 months.[1] The diagnosis of JIA was made according to the criteria from the International League against Rheumatism.[7;8] In cases of presumed JIA, the diagnosis was confirmed by a pediatric rheumatologist. The presence of other systemic diseases associated with uveitis was assessed according to current diagnostic criteria. The ocular pressure was measured using applanation tonometry, but if this was not possible, noncontact tonometry or the Tono-Pen (Medtronic Ophthalmics, Minneapolis, MN) was used. In 2 patients, it was necessary to evaluate intraocular pressure (IOP) under general anesthesia. Gonioscopic evaluation of the anterior chamber was performed only in selected patients, most of the time in older children. For young patients, this examination needs general anesthesia, which we try to avoid where possible. Secondary glaucoma was defined as the presence of pathologic cupping of the optic disc, a glaucomatous visual field defect with IOP higher than 21 mmHg, or both.[4] We defined OHT as 3 successive IOP measurements higher than 21 mmHg, single eye pressure higher than 30 mmHg (to exclude temporary or slight elevations of IOP), or any IOP higher than 21 mmHg for which glaucomatous treatment had been started in the absence of pathologic optic disc cupping or visual field changes.[9] In this study, the term elevated IOP encompasses both OHT and SG. Blindness was defined according to the World Health Organization criteria (profound vision loss, that is, visual acuity of less than counting fingers at 3 meters or a central visual field of less than 10°, or tunnel vision).[10] We analyzed the clinical data at the following points after the diagnosis of uveitis; 6 months and 1, 3, 5, 7, and 10 years.

Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS Inc., Chicago, IL). The Pearson chi-square test or the Fisher exact test (>20% of cells have an expected count of fewer than 5) were used to compare possible associations between categorical variables. A 1-way analysis of variance with the Bonferroni correction was used for multiple comparisons. We applied the binary logistic regression analysis to identify predictive factors. P values less than 0.05 were considered to be statistically significant.

Results

General characteristics. From a total of 173 patients with childhood uveitis, 147 patients were included in the analysis. Twenty-six patients were excluded from this study because no information about the IOP was available (n = 12) or follow-up was less than 6 months (n = 14). Bilateral disease was observed in 109 (109/147; 74%) patients, resulting in 256 affected eyes. The mean duration of follow-up was 5 years (range, 0.5–10 years). The number of patients followed up

Table 1. Study population

	6-mo Follow-up	1-yr Follow-up	3-yr Follow-up	5-yr Follow-up	10-yr Follow-up
No. of patients in follow-up	147	133	97	62	31
Mean age at onset of uveitis (yrs)	8.4	8.1	7.7	7.1	6.5

and the mean age of onset of uveitis at different time points are shown in Table 1. The boy-to-girl ratio was 4:6. Family history regarding glaucoma was known for 79 children, of whom 2 (3%) were positive for glaucoma. Information about ethnic background was available for 66 children: white, n = 46 (70%); Mediterranean, n = 10 (15%); Asian, n = 5 (8%); black, n = 5 (8%).

Elevated intraocular pressure. At 6 months after the diagnosis of uveitis, 21 of 147 (14%) children experienced elevated IOP in at least 1 eye (Table 2). The number of patients with elevated IOP increased during follow-up: 25 of 97 patients (26%) at 3 years, 22 of 62 patients (35%) at 5 years, and 12 of 31 patients (39%) at 10 years of follow-up. Secondary glaucoma was diagnosed in 8 of 97 patients (8%) at 3 years of follow-up (Table 2). At 5 years of follow-up, the percentage of children with uveitis in whom SG developed increased to 21% (13/62) and remained stable until the 10-year follow-up. After a follow-up of 5 years, 13 of 22 (59%) children with OHT experienced SG, and this percentage remained stable until the 10-year follow-up. The median length of time between the onset of uveitis and the development of elevated IOP (n = 54) was 1 year (mean, 1.9 years; range, 0–9 years; Fig 1).

No differences were found for developing IOP or SG between boys and girls, nor between different ethnic backgrounds. In children with elevated IOP, uveitis was bilateral in 23 of 25 (92%) and unilateral in 2 of 25 (8%) at the 3-year follow-up, compared with 50 of 72 (69%) children with bilateral uveitis and 22 of 72 (31%) children with unilateral uveitis in those who had no elevated IOP (p=.024).

Clinical course of uveitis. There were no significant differences for developing elevated IOP and SG between those with chronic or acute uveitis (Table 3).

Anatomic classification of uveitis. The number of patients with elevated IOP according to anatomic classification of ocular inflammation is shown in (Table 4). Although intermediate uveitis had the highest percentage of elevated IOP during follow-up, no significant differences were observed between the different anatomic localizations of uveitis. At the 5-year of follow-up, 4 of 9 children with

Table 2. Elevated intraocular pressure, secondary glaucoma, and ocular hypertension in pediatric uveitis

	6-mo Follow- up (n=147)			1-yr Follow-up (n=133)		
	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
No. of patients	18 (12)	3 (2)	21 (14)	20 (15)	4 (3)	24 (18)

Table 3. Elevated intraocular pressure, secondary glaucoma, and ocular hypertension according to course

	6-mo Follow-up (n=147)				1-yr Follow-up (n=133)			
	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
Acute uveitis	24	2 (8)	0 (0)	2 (8)	23	1 (4)	1 (4)	2 (9)
Chronic uveitis	123	16 (13)	3 (2)	19 (15)	110	19 (17)	3 (3)	22 (20)
P value			1.000	0.529			0.537	0.248

[a]If the divisor is less than 10, no percentages are shown.

Table 4. Elevated intraocular pressure, secondary glaucoma and ocular hypertension according to anato-

	6-mo Follow-up (n=147)				1-yr Follow-up (n=133)			
	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
Anterior uveitis	72	8 (11)	1 (1)	9 (13)	64	9 (14)	1 (2)	10 (16)
Intermediate uveitis	34	6 (18)	1 (3)	7 (21)	30	7 (23)	1 (3)	8 (27)
Posterior uveitis	22	3 (14)	0 (0)	3 (14)	21	2 (10)	1 (5)	3 (14)
Panuveitis	19	1 (5)	1 (5)	2 (11)	18	2 (11)	1 (6)	3 (17)
P value			0.322	0.528			0.214	0.512

[a]If the divisor is less than 10, no percentages are shown.

Table 5. Elevated intraocular pressure, secondary glaucoma, and ocular hypertension according to under-

	6-mo Follow-up (n=147)				1-yr Follow-up (n=133)			
	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
JIA	35	4 (11)	1 (3)	5 (14)	33	4 (12)	1 (3)	5 (15)
Toxoplasmosis	12	1 (8)	0[a]	1 (8)	11	0 (0)	1 (10)	1 (9)
Sarcoidosis	3	0[a]	0[a]	0[a]	3	0[a]	0[a]	0[a]
MS	1	0[a]	0[a]	0[a]	1	0[a]	0[a]	0[a]
Herpes	4	1[a]	0[a]	1[a]	4	1[a]	0[a]	1[a]
Fuchs' uveitis syndrome	5	0[a]	0[a]	0[a]	4	0[a]	0[a]	0[a]
Unknown	78	12 (15)	2 (3)	14 (18)	69	15 (22)	2 (3)	17 (25)
Others[b]	9	0[a]	0[a]	0[a]	8	0[a]	0[a]	0[a]

JIA=juvenile idiopathic arthritis; MS=multiple sclerosis; NA=not applicable.
[a]If the divisor is less than 10, no percentages are shown.
[b]Others: tubulointerstitial nephritis and uveitis (n=2), chronic infantile neurological cutaneous and articular/neonatal onset subacute neuroretinitis (n=1), toxic (n=1) and trauma (n=1).

3-yr Follow-up (n=97)			5-yr Follow-up (n=62)			10-yr Follow-up (n=31)		
Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
17 (18)	8 (8)	25 (26)	9 (15)	13 (21)	22 (35)	6 (19)	7 (23)	12 (39)

of pediatric uveitis

3-yr Follow-up (n=97)				5-yr Follow-up (n=62)				10-yr Follow-up (n=31)			
Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
14	0 (0)	1 (7)	1 (7)	10	0 (0)	1 (10)	1 (10)	3	0[a]	0[a]	0[a]
83	17 (20)	7 (8)	24 (29)	52	9 (17)	12 (23)	21 (40)	28	5 (18)	7 (25)	12 (43)
		1.000	0.107			0.673	0.082			1.000	0.265

mic classification in pediatric uveitis

3-yr Follow-up (n=97)				5-yr Follow-up (n=62)				10-yr Follow-up (n=31)			
Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
49	9 (18)	5 (10)	14 (29)	36	4 (11)	11 (31)	15 (42)	14	1 (7)	5 (36)	6 (43)
19	7 (37)	0 (0)	7 (37)	9	4[a]	0[a]	4[a]	6	2[a]	1[a]	3[a]
16	1 (6)	1 (6)	2 (13)	9	1[a]	1[a]	2[a]	4	0[a]	0[a]	0[a]
13	0 (0)	2 (15)	2 (15)	8	0[a]	1[a]	1[a]	7	2[a]	1[a]	3[a]
		0.474	0.114			0.067	0.055			0.119	0.380

lying cause of pediatric uveitis

3-yr Follow-up (n=97)				5-yr Follow-up (n=62)				10-yr Follow-up (n=31)			
Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
29	7 (24)	4 (14)	11 (38)	24	3 (13)	9 (38)	12 (50)	12	1 (8)	4 (33)	5 (42)
9	0[a]	1[a]	1[a]	5	0[a]	1[a]	1[a]	2	0[a]	0[a]	0[a]
3	0[a]	0[a]	0[a]	2	0[a]	0[a]	0[a]	2	1[a]	0[a]	1[a]
1	0[a]	0[a]	0[a]	1	0[a]	0[a]	0[a]	1	0[a]	0[a]	1[a]
2	0[a]	0[a]	0[a]	1	0[a]	0[a]	0[a]	1	0[a]	0[a]	0[a]
4	0[a]	0[a]	0[a]	2	0[a]	0[a]	0[a]	0	NA	NA	NA
44	10 (23)	3 (7)	13 (30)	27	6 (22)	3 (11)	9 (33)	13	2 (15)	3 (23)	5 (38)
5	0[a]	0[a]	0[a]	0	NA	NA	NA	0	NA	NA	NA

multisystem inflammatory disease syndrome (n=2), psoriasis (n=1), acute multifocal placoid pigment epitheliopathy (n=1), diffuse unilateral

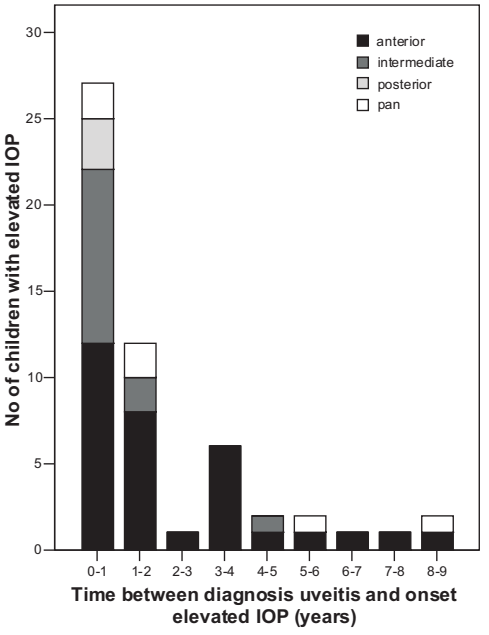

Figure 1. Bar graph showing the time taken to reach elevated intraocular pressure (IOP) after diagnosis of uveitis.

intermediate uveitis had OHT, but none of these patients progressed to SG (0/4; 0%), whereas 11 of 15 (73%) children with anterior uveitis and OHT progressed to SG (p=.018).

The mean time between the onset of uveitis and the start of elevated IOP for the 4 different locations of uveitis is illustrated in Figure 1. Posterior and intermediate uveitis had a shorter interval between the clinical onset of uveitis and onset of elevated IOP (0.3 and 0.9 years, respectively) compared with anterior and panuveitis (2.3 and 2.9 years, respectively; p=.025, log-rank test): anterior versus intermediate uveitis (p=.016) and posterior uveitis (p=.010) and panuveitis versus posterior uveitis (p=.024).

Specific uveitis entities. A systemic disease was observed in 44 of 147 (30%) patients; the specific systemic and ocular diagnoses are shown in (Table 5).

Juvenile idiopathic arthritis. Juvenile idiopathic arthritis was the most commonly associated systemic disease (35/147; 24%) of the total population and formed the underlying disease for 35 (35/72; 49%) children with anterior uveitis. All children with JIA-associated uveitis had chronic anterior uveitis.

After 5 years of follow-up, no difference was found in developing elevated IOP between children with JIA-associated uveitis and children with uveitis not

associated with JIA. However, SG was significantly more often noted in children with JIA-associated uveitis (9/24; 38%) compared with children with other uveitis entities (4/38; 11%) at the 5-year follow-up (p=.022).

No differences in the development of elevated IOP (5/9; 56%) or SG (3/9; 33%) were found in children with JIA with onset of uveitis before the onset of arthritis compared with children with JIA in whom uveitis developed later on during the disease process (elevated IOP, 7/15 [47%]; or SG, 6/15 [40%]; not significant).

Antinuclear antibodies. Of the 40 patients tested for the presence of ANAs, 24 were positive: 19 patients with JIA-associated uveitis and 5 patients with uveitis of unknown cause after 5 years of follow-up. Fourteen of the 24 (58%) ANA-positive children had elevated IOP compared with 5 of 16 (31%) ANA-negative children during a follow-up of 5 years (p=.093). Secondary glaucoma was significantly more often observed in ANA-positive children (10/24; 42%) than in ANA-negative (1/16; 6%) children at 5 years of follow-up (p=.027). For the ANA-positive patients, there was no difference found between JIA-associated uveitis and uveitis of unknown origin in developing elevated IOP or SG.

Lens extraction. Twenty-eight eyes had undergone lens extraction and had a follow-up of 3 years after surgery. Seven of these eyes (7/28; 25%) had preexisting elevated IOP. Of the remaining 21 eyes, 38% (8/21) experienced elevated IOP and 19% (4/21) experienced SG within 3 years after lens extraction. All the eyes had anterior uveitis except for 1 case of panuveitis, and in 17 of 21 eyes, the uveitis was associated with JIA. Eyes of patients with JIA-associated uveitis had less SG after cataract surgery than eyes of patients with anterior uveitis not associated with JIA (1/17 [6%] vs. 3/3 [100%]; p=.004).

Periocular or systemic corticosteroids. Eyes treated with periocular corticosteroid injections more frequently experienced elevated IOP than eyes not treated with corticosteroid injections (Table 6). Secondary glaucoma was observed more frequently after periocular corticosteroid injections than in patients not treated with periocular injections only at 6 months of follow-up (3/43 eyes vs. 1/213 eyes; p=.016). The number of injections had no influence on the development of elevated IOP (1-way analysis of variance, Bonferroni, not significant).

In children with JIA-associated uveitis, there was no difference in elevated IOP (3/15 eyes; 20%) and SG (2/15 eyes; 13%) development after periocular corticosteroid injections compared with patients without injections (elevated IOP, 15/40 eyes [38%]; p=.335; and SG, 4/40 eyes [10%]; p=.660) during a follow-up of 3 years.

During a follow-up of 3 years, eyes with intermediate uveitis (19/33; 58%) received more periocular corticosteroid injections than eyes with anterior uveitis (19/85;

Table 6. Elevated intraocular pressure, secondary glaucoma, and ocular hypertension according to peri-

	6-mo Follow-up (n=256)				1-yr Follow-up (n=234)			
	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
Injection +	43	8 (19)	3 (7)	11 (26)	51	12 (24)	3 (6)	15 (29)
Injection -	213	16 (8)	1 (0)	17 (8)	183	17 (9)	3 (2)	20 (11)
P value			0.016	0.001			0.119	0.001

Table 7. Blind *eyes* in patients with pediatric uveitis

	6-mo Follow-up	1-yr Follow-up	3-yr Follow-up	5-yr Follow-up	10-yr Follow-up
No. of patients	147	133	97	62	31
Patients with unilateral blind *eye* resulting from SG (%)	0 (0)	0 (0)	1 (1)	1 (2)	3 (10)
Total no. of patients with unilateral blind *eye* (%)	1 (1)	4 (3)	4 (4)	4 (6)	9 (29)
JIA	0	1	1	1	4
Unknown	1	3	3	3	4
MS	0	0	0	0	1

JIA=juvenile idiopathic arthritis; MS=multiple sclerosis; SG=secondary glaucoma.
No patients with bilateral blind *eyes* were found.

22%), posterior uveitis (2/24; 8%), and panuveitis (5/25 [20%]; p<.05, 1-way analysis of variance, Bonferroni). In children with intermediate uveitis, during 3 years of follow-up, there tended to be more cases of elevated IOP after periocular corticosteroid administration than in children not receiving corticosteroid injections (9/19 *eyes* [48%] vs. 2/14 *eyes* [14%]; p=.067), although this did not reach significance. However, no SG was found in children with intermediate uveitis treated with periocular corticosteroid injections (n=19 *eyes*) and not treated with corticosteroid injections (n=14 *eyes*) during a follow-up of 3 years.

Systemic corticosteroids were of no influence on the development of elevated IOP or SG.

Secondary glaucoma and visual outcome. One blind *eye* (1/256, 0%) was observed at the onset of uveitis and 10 blind *eyes* were observed during follow-up, all unilateral (Table 7). These blind *eyes* had a mean follow-up of 3.5 years (range, 0.0–7.8 years). Blind *eyes* resulting from SG were present in 3 of them, all with chronic, bilateral, ANA-positive uveitis and associated with JIA (n=2) or uveitis of

ocular corticosteroid injections

3-yr Follow-up (n=137)				5-yr Follow-up (n=109)				10-yr Follow-up (n=57)			
Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)	Total n	Ocular hypertension, n (%)	Secondary glaucoma, n (%)	Elevated intraocular pressure, n (%)
45	11 (24)	5 (11)	16 (36)	27	8 (30)	3 (11)	11 (41)	20	5 (25)	6 (30)	11 (55)
122	17 (14)	7 (6)	24 (20)	82	8 (10)	13 (16)	21 (26)	37	3 (8)	5 (14)	8 (22)
		0.233	0.033			0.756	0.134			0.342	0.003

unknown origin (n=1). Other causes of blindness were: cystoid macular edema (n=1), optic atrophy in multiple sclerosis (n = 1), exudative retinal detachment (n=1), subretinal neovascularization (n = 1), and diverse surgical complications (n=3).

Discussion

Our study shows that children with JIA-associated uveitis are at higher risk of experiencing SG compared with children with uveitis not associated with JIA after a follow-up of 5 years (p<.022). The risk of development of OHT was similar for all the pediatric uveitis entities included. Additional risk factors for SG in pediatric uveitis were periocular corticosteroid injections shortly after the onset of uveitis and positive ANA status. The number of periocular injections, however, was of no influence on the development of elevated IOP. For children with JIA-associated uveitis, these additional risk factors, such as corticosteroid injections and positive ANA, were not associated with the development of elevated IOP or SG. These observations reveal that JIA itself forms an independent risk factor for developing SG. Sex, race, localization, chronic or acute course of uveitis, and the administration of systemic corticosteroids had no influence on the development of elevated IOP or SG in pediatric uveitis. This is in contrast with SG in adult uveitis patients, where SG occurred more frequently with chronic uveitis.[11] Previously, it was reported that girls with JIA are at higher risk of developing uveitis, but boys with uveitis have more complications and are at risk of a poor visual outcome.[12;13] In our study, however, gender had no influence on developing elevated IOP or SG. We found similar percentages of elevated IOP (OHT, SG, or both) as those mentioned in the study of Rosenberg *et al*, who observed SG, OHT, or both in 11.4%, 15.3%, 24.1%, 30.8%, and 45.5% during a follow-up of, respectively, 6 months, 1, 3, 5, and 10 years in children with uveitis.[14] Our study population comprised a population similar to that of the study by Rosenberg *et al* concerning sample size, gender, bilateralism, and age at diagnosis of uveitis. Rosenberg *et al* compared

their study population with several other series and concluded that their results were representative of pediatric uveitis in general. Although our study population is similar to that of Rosenberg *et al*, we cannot entirely exclude that the severity of the disease has led to a follow-up bias. Children with more severe uveitis might have come for a longer follow-up. The baseline features (localization and course of uveitis and number of patients requiring systemic treatment) of patients with short (<5 years) and long (>5 years) follow-up did not differ. However, the number of patients with JIA-associated uveitis was significantly higher in the group of patients with follow-up longer than 5 years. The study by Chalom *et al* showed that ANA-positive children experienced uveitis more frequently, but ANA-negative children with uveitis had more ocular complications.[15] This seems to be in contrast to our findings, in which SG occurred more frequently in ANA-positive uveitis. However, Chalom *et al* did not specify the different complications (synechiae, cataract, band keratopathy, and glaucoma), and the exact percentages of SG are not reported. This may explain the discrepancy between their and our observations. The observation that none of the patients with elevated IOP with intermediate uveitis progressed to SG compared with one third of the patients with anterior uveitis may indicate that elevated IOP in intermediate uveitis is probably more temporary, less threatening, or both, than elevated IOP in anterior uveitis. In our population, borderline association between elevated IOP and corticosteroid injections in children with intermediate uveitis was observed during a follow-up of 3 years. In addition, periocular corticosteroid injections were administered more frequently in this group than in other anatomical types of uveitis. From our data, it is not obvious whether treatment with periocular corticosteroid injections was responsible for elevated IOP or whether these children, treated with injections, had a more severe uveitis resulting in damage to the trabecular meshwork, ciliary body, or both. The observation that multiple corticosteroid injections did not increase further the risk of elevated IOP supports the hypothesis that the ocular damage resulting from uveitis may be responsible for elevated IOP, but it also may indicate that elevated IOP after periocular corticosteroid injection is linked to an individual high responder. The observation that the association between corticosteroid injections and elevated IOP was not present at all time points may be explained by the fact that the development of elevated IOP in uveitis is dependent on several factors, of which corticosteroid injections is only one.

Two thirds of all children with OHT or SG experienced elevated IOP in the first 2 years after the onset of uveitis, but elevated IOP also can manifest itself after a more extended interval after the onset of uveitis, which makes it very imperative to check the IOP regularly. Although there were no significant differences

between the 4 different anatomical localizations of uveitis in developing elevated IOP, posterior and intermediate uveitis had a significantly shorter interval between the diagnosis of uveitis and the onset of elevated IOP compared with anterior and panuveitis. This discrepancy may be explained in part by the fact that children with intermediate uveitis received more periocular corticosteroid injections. In our series, SG seemed not to be negatively influenced by previous lens extraction. When we roughly compare these results with the risk of developing SG in phakic children at 5 years of follow-up, we find no major differences. However, this issue can be investigated only in a randomized study in which half of the children with cataract would undergo surgery and the other half would not, which is not feasible. Whether the risk of SG after cataract surgery is related to surgical techniques, IOL implantation, or anterior vitrectomy is a subject for further study. Previously, we reported that SG was one of the major causes of blindness in children with uveitis.[1] In our study, one third of the blind eyes were caused by SG, which emphasizes the seriousness of this complication. However, the number of blind eyes, which is roughly 7% (11/147) of the total population, was much less compared with that of the study of Kanski and Shun-Shin.[2] Explanations for this decrease of visual loss among children with uveitis may be the introduction of new glaucoma medications, improved surgical techniques, or better immunosuppressive treatments of uveitis. Furthermore, one should always be aware of the risk of amblyopia developing in children with uveitis. In our series, none of the blind eyes was caused by amblyopia. New specialized research tools, such as optic nerve head or nerve fiber layer analysis by optical coherence tomography and central corneal thickness measurement, are very important for monitoring and detecting elevated IOP in children with uveitis. However, because of the retrospective character of our study, these new techniques were neither performed systematically nor available. Optical coherence tomography is a relatively easy and quick research method, and therefore is very suitable for investigating children. The value of optical coherence tomography and central corneal thickness in IOP in children has to be determined, but we would certainly consider using these new techniques for all children with OHT and SG in the future. Visual field testing is not easy to perform in children. Especially in young children, the compliance during visual field testing is low. For the future, we are planning to use more fully automated visual field testing. We used the van Herick technique to evaluate the anterior chamber depth, which is easy to perform in children. In conclusion, the most important risk factor for the development of SG in pediatric uveitis is JIA, in addition to ANA-positive uveitis without evidence of arthritis. We recommend that IOP always be measured and regularly checked in all children with uveitis.

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Chapter 3

Trabeculectomy versus Ahmed glaucoma valve implant in children with juvenile idiopathic arthritis-associated uveitis

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(Submitted for publication)

Abstract

Purpose: To evaluate the outcome of trabeculectomy (TE) versus Ahmed glaucoma valve (AGV) implant in children with juvenile idiopathic arthritis (JIA)-associated uveitis.

Design: Retrospective cohort study.

Methods: Thirty-three eyes of 19 children with JIA-associated uveitis who underwent TE (n=27) or AGV implantation (n=13; of which 7 prior TE) before the age of 20 years were enrolled in this institutional study. The medical records of all included patients were evaluated. Main outcome measures were surgical success, defined as postoperative intraocular pressure (IOP) of < 22 mmHg and ≥ 5 mmHg with or without antiglaucoma medications and without loss of light perception and no need for further surgical intervention for glaucoma.

Results: Kaplan-Meier survival analysis showed no permanent failures in the AGV group and a mean survival time of 4.7 years for the TE group (p=.009). Kaplan-Meier survival analysis for the AGV group and the phakic eyes of the TE group showed similar results (p=.229), but indicated better outcomes for the AGV eyes compared to TE eyes which underwent cataract extraction before or after the TE (p=.002). The mean survival time for the phakic eyes of the TE group was 7.51 years.

Conclusions: The implant of a primary AGV in aphakic or pseudophakic eyes of children with JIA-associated uveitis represents a better treatment option than TE. In phakic eyes of children with JIA-associated uveitis, primary TE can postpone the need for the implantation of an AGV by approximately 7.5 years.

Introduction

Glaucoma is a major problem in childhood uveitis. Previously, we found secondary glaucoma (SG) in 20% of all children with uveitis and almost twice as much in children with juvenile idiopathic arthritis (JIA)-associated uveitis (38%) after 5 years of uveitis.[1] Kanski and Shun-Shin reported in 1984 that 1 out of 3 glaucomatous eyes of children with JIA-associated uveitis lost perception of light.[2] In 2000, it was reported that still 12% of all children with JIA-associated uveitis became blind.[3] Therefore the treatment of SG in this specific population is challenging. One of the reasons for the poor prognosis is the presence of many risk factors for the failure of trabeculectomy (TE) in this population, including the intraocular inflammation, young age, previous cataract surgery, and prolonged duration of antiglaucoma medications.[4-6] One study showed more promising results in this specific patient group with glaucoma drainage devices (Molteno implant).[7] The Ahmed glaucoma valve (AGV) is nowadays a commonly used glaucoma drainage device worldwide and the results in adult uveitis patients are favorable.[8;9] The efficiency of AGV in children with uveitis was reported to our knowledge in only one study of 7 eyes, which showed promising results.[10] In the present study we compared the outcomes of AGV implantations with the outcomes of TE in children with JIA-associated uveitis.

Methods

In this institutional retrospective study we reviewed the medical records of 19 children with JIA-associated uveitis and SG requiring surgery. These children were identified in a complete database search of the Department of Ophthalmology, University Medical Center, Utrecht, the Netherlands between October 1998 and June 2007. Only those patients with an onset of JIA-associated uveitis before the age of 16 years and glaucoma surgery (TE and/or AGV) performed during childhood (2-9 years of age) or puberty (10-19 years of age) at our institute with a minimal follow-up of 6 months were included in this study. Only the results of first TE or AGV per eye were analyzed. Our center combines a secondary and a tertiary referral function. Children were referred by the ophthalmologists of secondary referral hospitals or by the pediatric rheumatologists of our medical center. The pediatric rheumatologists referred children for uveitis screening according to the criteria of the American Academy of Pediatrics in cases of JIA or other systemic diseases.[11] Diagnosis of uveitis was based on the criteria of the Standardization of Uveitis Nomenclature (SUN) Workshop.[12] The diagnosis

of JIA was made according to the criteria from the International League against Rheumatism (ILAR) and confirmed by a pediatric rheumatologist.[13;14] We recorded the following clinical data for each patient: gender, race, age at onset of uveitis, age at first AGV implantation or first TE, the use of wound-healing modulators such as 5-fluorouracil (5-FU) and mitomycin C (MMC) and duration of application, cataract surgery, all other intraocular surgeries and ocular complications before glaucoma surgery. Pre- and postoperatively at 3 months, 6 months, and 1, 2, and 3 years, we recorded visual acuity, intraocular pressure (IOP), cup-disc ratio (C/D) and color of the optic disc, number of topical antiglaucoma medications and oral tablets of acetazolamide and all intraocular surgeries and complications. The optic disc was evaluated by ophthalmoscopy. The intraocular pressure was measured with applanation tonometry, but if this was not possible, non-contact tonometry or the Tono-Pen was used. The optic nerve head was scored as pathological when the C/D was 0.7 or greater, when there was a pallor/cup discrepancy, when there was a C/D difference of greater than 0.2 between fellow-eyes or when there was an increase of the C/D of more than 0.2 compared with earlier assessments.[15] Surgical success was defined as postoperative IOP of < 22 mmHg and ≥ 5 mmHg with or without antiglaucoma medications and without loss of light perception and no need for further surgical intervention for glaucoma. Minor revisions, including laser suture lysis, needling of the bleb, additional suturing with restoration of anterior chamber and ligation of the tube, during the first 6 weeks postoperatively were not considered as failure of glaucoma surgery. Incidental hypotony (< 5 mmHg) or hypertony (≥ 22 mmHg) was scored as a transient failure. The AGV (model S-2, New World Medical, Inc, Rancho Cucamonga, California, USA) implantation and TE were both performed under general anesthesia by 1 of 2 attending physicians of the Department of Ophthalmology, University Medical Center, Utrecht, the Netherlands (JHdB or JSS). During TE surgery, MMC was applied in 25 eyes (median 2 minutes, range 1 to 4 minutes), 5-FU in 1 eye (3 minutes) and in 1 eye no wound-healing modulators were used during surgery. No wound-healing modulators were used in the AGV group. All patients were pretreated with systemic corticosteroids (1 mg/kg) starting 1 day to 1 week before surgery and during surgery with periocular bethametason. The shield of systemic corticosteroids was slowly tapered down depending on ocular features following glaucoma surgery.

Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS Inc., Chicago, IL). The Mann-Whitney U test was used to compare the means of the (non-parametric) different groups. The Pearson Chi-square test or the Fischer's exact test was used to compare possible

associations between categorical variables where appropriate. Success rates were compared using Kaplan-Meier survival curves and the log rank test. P values less than .05 were considered to be statistically significant.

Results

General characteristics. Of a total of 276 children with uveitis 74 (27%) had JIA-associated uveitis of whom 21 (28%) children were operated on for SG (36 eyes). Nineteen children (33 eyes) fulfilled our criteria for inclusion and underwent TE (17 patients, 27 eyes) or AGV implantation (10 patients, 13 eyes). Seven of 13 eyes with an AGV had prior one or two TEs. No statistically significant difference was found between both groups concerning the male to female ratio (p=.706), the age at the diagnosis of uveitis (p=.289) and the age at the diagnosis of arthritis (p=.631). All patients were of European origin, except one girl who was of African origin and underwent TE on 1 eye. **Trabeculectomy.** In 17 children (27 eyes) a TE was performed at a median age of 9.1 years. Transient complications during the first 6 weeks after surgery are shown in Table 1. The phakic status during follow-up of all eyes is shown in Table 2. We found a mean survival time (duration of success of the TE) of 7.51 years for phakic eyes, 1.96 years for eyes with cataract extraction before TE and 2.81 years for eyes with cataract extraction after TE (p=.098; Figure 1). Of the total group, two years after TE, 12 out of 25 eyes (48%, 2 eyes were lost to follow-up) failed due to loss of the function of the bleb. Eleven of these 12 eyes (92%) had undergone cataract extraction (4 eyes before TE and 7 eyes after TE). In the successful eyes (n=23), the median IOP decreased from 35 mmHg preoperatively to 11 mmHg (median decrease of 21mmHg, 60%) directly after surgery and remained approximately the same during 3 years of follow-up (Table 3). The number of eyes with a pathological optic nerve head was 58% (15/26 eyes) preoperatively. Two years later, 5 additional successful eyes had a pathological optic nerve head. Three months after surgery, the preoperatively pathological optic nerve head was shown to be temporarily reversible in 54% of the eyes (7/13 eyes; 2 failures). After 1 year, the optic nerve head of 3 eyes (3 out of 7) became again pathologically despite normal IOP (< 22 mmHG). During follow-up 15 failures were observed. Of those failures, 9 eyes received an AGV and 2 eyes received a Baerveldt implantation, 3 eyes underwent a successful second TE and 1 eye had slightly elevated IOP during follow-up under treatment with topical antihypertensive agents. **Ahmed glaucoma valve**. An AGV was implanted in 13 eyes (10 patients) at a median age of 13.5 years. Seven eyes (54%) were previously operated on

Table 1. Transient complications of the successful eyes during the first 6 weeks after glaucoma surgery in children with juvenile idiopathic arthritis-associated uveitis

	Trabeculectomy 23 eyes[a]	Ahmed glaucoma valve 13 eyes	P value
Flat anterior chamber	4 17%	1 8%	0.634
Hypotony syndrome[b]	6 26%	5 38%	0.475
Choroidal effusion and/or (bullous) detachment	8 35%	4 31%	1.000
Decompression retinopathy	9 39%	0 0%	0.014
Conjunctival defect / Wound leak	3 13%	1 8%	1.000
IOP≥22 mmHg	5 22%	0 0%	0.136
Hyphema	2 9%	0 0%	0.525

IOP=intraocular pressure.
[a]Four failures were excluded.
[b]Edema of optic nerve head and/or maculopathy due to hypotony.

Table 2. Cataract extraction of all included eyes before and after glaucoma surgery in patients with juvenile idiopathic arthritis-associated uveitis

	Trabeculectomy 27 eyes	Ahmed glaucoma valve 13 eyes	P value
Cataract extraction before glaucoma surgery	6 (22%)	12 (92%)	<0.001
Cataract extraction after glaucoma surgery during follow-up	12 (44%)	0 (0%)	0.004
No cataract extraction during complete follow-up	9 (33%)	1 (8%)	0.124

for glaucoma (single TE n=5, more than 1 TE n=2). Transient complications during the first 6 weeks after surgery are shown in Table 1. During follow-up no permanent failures occurred, however 4 eyes had 1 or 2 episodes of transient failure (Table 4). Before AGV surgery the median IOP was 31 mmHg and diminished by 14 mmHg (median, 45%) postoperatively (Table 4). The number of eyes with a pathological optic nerve head was 75% (9/12 eyes tested) preoperatively. Three months after surgery 25% (2/8 eyes; 1 temporarily failure) of these pathological optic nerve heads were shown to be reversible.

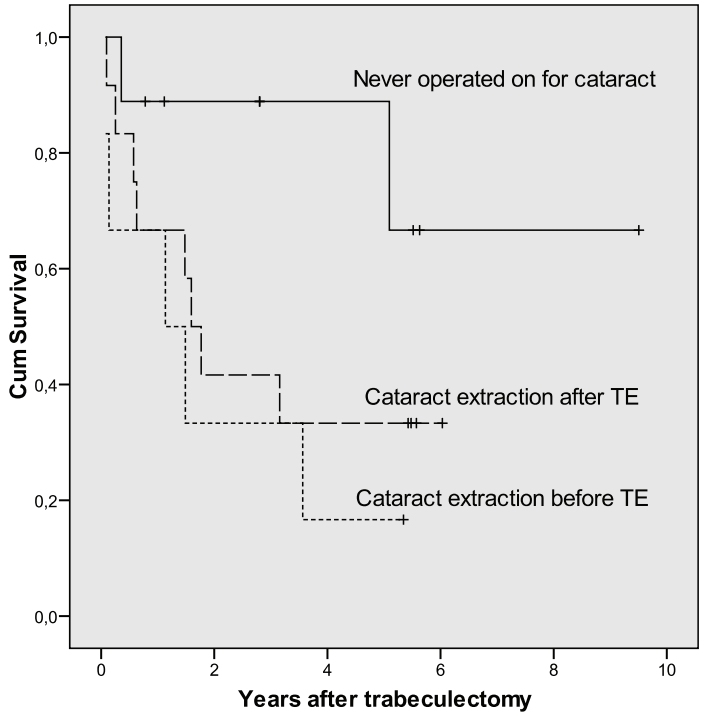

Figure 1. Kaplan-Meier survival plots for eyes with cataract extraction before trabeculectomy, eyes with cataract extraction after trabeculectomy and for phakic eyes of children with juvenile idiopathic arthritis-associated uveitis. Surgical success was defined as postoperative IOP of < 22 mmHg and ≥ 5 mmHg with or without antiglaucoma medications and without loss of light perception and no need for further surgical intervention for glaucoma. P=.1148, log rank test.

TE versus AGV. No permanent failures were found in the AGV group and the mean survival time was 4.7 years in the TE group (p=.009). Figure 2 demonstrates the Kaplan-Meier survival analysis for all subjects. Transient complications during the first 6 weeks after surgery were similar in both groups except for decompression retinopathy which only occurred in the TE group (39%; p=.014; Table 1). Two years after glaucoma surgery the median IOP was similar in both groups (13 mmHg versus 11 mmHg, p=.647) and the number of successful eyes was 13 out of 25 (52%) in the TE group compared with 7 out of 8 (1 transient failure) eyes (88%) in the AGV group (p=.108). No significant difference was found between both groups concerning the numbers of eyes needing topical or oral antihypertensive agents and the number of eyes with a pathological optic disc 2 years after surgery. Success without additional antiglaucoma medications after 1 year of follow-up was

Table 3. Intraocular pressure, optic nerve head and antiglaucoma medications before and after trabeculectomy in children with juvenile idiopathic arthritis-associated uveitis

	No. of included eyes	No. of excluded eyes (end of FU and failures)	No. of eyes with a pathological optic nerve head (%)	Median IOP (mmHg) (range)	Topical antihypertensive agents		Oral tablets of acetazolamide (250 mg)
					no. of treated eyes (%)	median no. of drops per eye (range)	no. of patients (%)
Preoperatively	27	NA	15 (58)[b]	35 (13-50)	27 (100)	4 (1-5)	17 (63)
3 months postoperatively	23[a]	4 bleb failures	7 (33)[b]	11 (6-20)	5 (22)	0 (0-2)	0 (0)
6 months postoperatively	22	5 bleb failures	7 (33)[b]	12 (6-21)	4 (18)	0 (0-2)	0 (0)
1 year postoperatively	19	1 end of FU 7 bleb failures	9 (47)	14 (6-21)	4 (21)	0 (0-4)	1 (5)
2 years postoperatively	13	2 end of FU 12 bleb failures	9 (69)	13 (9-20)	3 (23)	0 (0-1)	1 (8)
3 years postoperatively	11	4 end of FU 12 bleb failures	7 (64)	11 (6-19)	3 (27)	0 (0-2)	2 (18)

FU=follow-up; IOP=intraocular pressure; NA=not applicable; No.=number.
[a]Six eyes underwent successful minor revision within the first 6 weeks postoperatively, including suture lysis (n=4) and needling of the bleb (n=2).
[b]The optic nerve head could not be evaluated in 1 eye preoperatively and at 6 months follow-up and in 2 eyes at 3 months follow-up due to cataract.

Table 4. Intraocular pressure, optic nerve head and antiglaucoma medications before and after Ahmed glaucoma valve implantation in children with juvenile idiopathic arthritis-associated uveitis

	No. of included eyes	No. of excluded eyes (end of FU and failures)	No. of eyes with a pathological optic nerve head (%)	Median IOP (mmHg) (range)	Topical antihypertensive agents		Oral acetazolamide 250 mg
					no. of treated eyes (%)	median no. of drops per eye (range)	no. of patients (%)
Preoperatively	13	NA	9 (75)[b]	31 (11-44)	13 (100)	4 (2-4)	5 (38)
3 months postoperatively	10[a]	1 transient hypertony 2 transient hypotony[c]	6 (60)	15 (9-20)	5 (50)	0.5 (0-1)	0 (0)
6 months postoperatively	12	1 transient hypertony	7 (64)[b]	14 (8-20)	4 (33)	0 (0-1)	0 (0)
1 year postoperatively	11	2 end of FU	7 (70)[b]	8 (6-17)	7 (64)	1 (0-4)	0 (0)
2 years postoperatively	8	1 transient hypotony[c] 4 end of FU	5 (71)[b]	11 (6-15)	3 (38)	0 (0-4)	1 (13)

FU=follow-up; IOP=intraocular pressure; NA=not applicable; No.=number.
[a]One eye underwent successful minor revision within the first 6 weeks postoperatively (additional suturing with restoration of anterior chamber).
[b]The optic nerve head could not be evaluated in 1 eye due to cataract.
[c]One eye had 2 episodes of transient failure (hypotony).

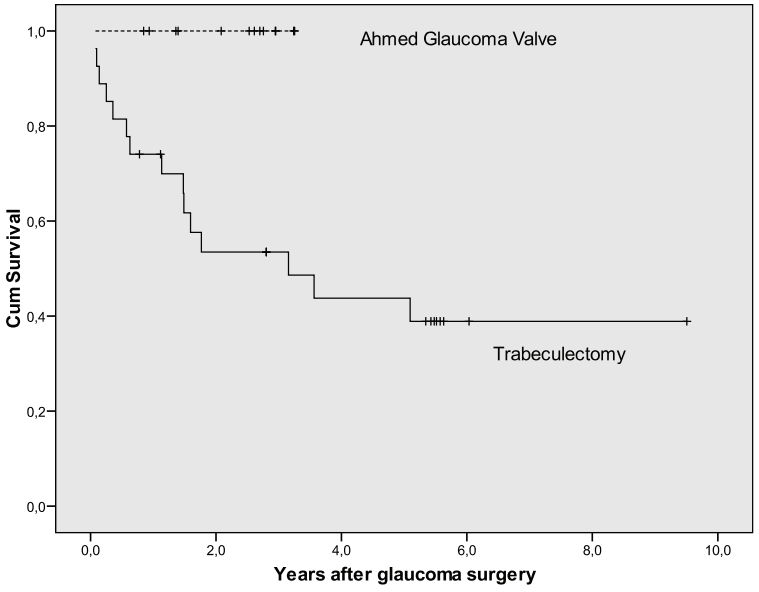

Figure 2. Kaplan-Meier survival plots for trabeculectomy and for Ahmed glaucoma valve implantation in eyes of children with juvenile idiopathic arthritis-associated uveitis. Surgical success was defined as postoperative IOP of < 22 mmHg and ≥ 5 mmHg with or without antiglaucoma medications and without loss of light perception and no need for further surgical intervention for glaucoma. P=.0102, log rank test.

15 out of 26 eyes (58%) versus 4 out of 11 eyes (36%, p=.295) and after 2 years 9 out of 25 eyes (36%) versus 5 out of 8 eyes (63%, p=.238) in the TE and AGV group, respectively. The patients in the AGV group where significantly older than the patients in the TE group (13.5 years versus 9.1 years respectively, p=.006). However, the oldest 13 eyes of the TE group had a median age at surgery of 11.6 years, which is comparable with the AGV group (13.5 years, p=.511). Kaplan-Meier survival analysis of these 2 groups showed also a significant difference for survival in favour of the AGV group (p=.035).

The number of phakic eyes at the time of glaucoma surgery differed between the AGV and TE group (1/13 versus 21/27 respectively, p<.001). In the TE group, phakic eyes had the longest survival (mean 7.51 years). When we compared all phakic eyes of the TE group with all eyes of the AGV group no difference in survival was found (p=.229). However, when we compared all eyes operated on for cataract of the TE group with the AGV group, a significant difference in survival was found (p=.002).

None of the included eyes of both groups ended blind during follow-up.

Discussion

In our study, the implantation of an AGV in children with SG due to JIA-associated uveitis was associated with a longer survival than performing TE. No permanent failures in the AGV group were observed during the first 2 years of follow-up in contrast to 48% in the TE group. However, success without antiglaucoma medications was similar in both groups at 1 and at 2 years of follow-up. The limited survival of TE in children with JIA-associated uveitis did not count for TE performed in phakic eyes, since these eyes had a comparable duration of survival as the AGV group. A longer duration of success for TE in phakic eyes than in aphakic and pseudophakic eyes was also previously noted.[6;16] In view of these findings, one might conclude that TE is not advisable in pseudophakic or aphakic eyes of children with JIA-associated uveitis. However, in phakic eyes of children with JIA-associated uveitis, TE was successful for approximately 7.5 years and therefore it might be concluded that TE in phakic eyes can postpone the eventual implantation of AGV for approximately 7.5 years. This possible delay might have a positive effect on potential long-term complications of AGV, such as tube migration due to eye growth, tube-cornea touch, corneal decompensation and the risk of endophthalmitis in the young children. However, one should always consider the pros and cons of primary AGV implantation or primary TE against each other. So far, no long-term information is available about AGV in eyes of children with JIA-associated uveitis. Although Souza reported a cumulative probability of success of only 49% with the AGV after 5 years in eyes with refractive glaucoma (27% uveitic glaucoma, 22% neovascular glaucoma, 19% other open-angle glaucoma and 32% other secondary angle-closure glaucoma) in where the eyes with uveitic glaucoma were at less risk of failure.[17] Since the poor results of trabeculectomy, one might consider an AGV as the primary surgery for glaucoma in pseudophakic, aphakic and cataractous eyes of children with JIA-associated uveitis.

Performing glaucoma surgery in children with uveitis, absolute abolishing of inflammation in the perioperative period is crucial for the success of surgery and to minimize the risk of hypotony. Therefore, all our patients were treated with systemic and/or periocular corticosteroid injections perioperatively to minimize the inflammatory response. In the case of TE, wound-healing modulators (MMC and 5-FU) were used to minimize scarring of the filtration bleb (fibrosis and vascular ingrowth).

Limitations of this study are the limited number of eyes with AGV implantation included and the relatively short follow-up. We do understand that there is a potential bias inherent in analyzing both eyes of one patient; however we prefer to

present our data on all eyes operated for SG, just as most prior studies of glaucoma drainage devices do in the literature. Another limitation is the possible bias due to difference in age at time of glaucoma surgery, which might have caused the better results of AGV. However, when we restricted the TE group to the oldest patients, still a significant difference was observed in favor of the AGV group.

Up to now, it is still not known which glaucoma device implant is favorable in the case of SG in JIA-associated uveitis. In a recently published study of Goulet III *et al* the AGV was compared with the Baerveldt 250-mm2 glaucoma implant and AGV was shown to be less effective.[18] However, this was based on an adult study population of which only a minority had uveitis-related SG. SG related to JIA-associated uveitis is thought to result from trabecular scarring, sclerosis or both caused by chronic trabeculitis.[10] Furthermore, uveitic eyes in JIA have marginally functioning ciliary bodies due to chronic inflammation. This means that many of these eyes are at risk of developing hypotony after glaucoma surgery. So far, the AGV seems to be able to reduce the IOP in these patients with a little risk of hypotony. Whether the Baerveldt 250-mm2 is suitable for SG in children with JIA-associated uveitis without inducing hypotony needs further investigation. In our clinic we have no experience with the Baerveldt 250-mm2 in children with JIA-associated uveitis, but severe hypotony was observed in both children in our clinic who received a Baerveldt 350-mm2. The future comparison of various glaucoma implant devices in a JIA-associated uveitis population would be of value, but due to limited number of patients a multi-center study would probably be required.

In conclusion, the implant of a primary AGV in aphakic or pseudophakic eyes of children with JIA-associated uveitis represents a better treatment option than TE. In phakic eyes of children with JIA-associated uveitis, primary TE can postpone the need for the implantation of an AGV by approximately 7 and a half years.

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Chapter 4

Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis

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Abstract

Purpose: To identify the possible risk factors for the development of cataract requiring surgery in children with juvenile idiopathic arthritis (JIA)-associated uveitis.

Design: Retrospective cohort study.

Methods: Data of 53 children with JIA-associated uveitis, of whom 27 had undergone cataract extraction (CE), were obtained. The main outcome measure, the interval between the onset of uveitis and the first CE (U–CE interval), was examined in relation to clinical and ophthalmologic characteristics and treatment strategies before CE.

Results: A shorter U–CE interval was found for children with posterior synechiae vs those without posterior synechiae (hazard ratio [HR], 3.57; 95% confidence interval [CI], 1.33 to 10.00). No significant difference was found for children in whom the uveitis was the first manifestation of JIA vs those in whom arthritis was the first manifestation of JIA (HR, 1.59; 95% CI, 0.63 to 4.00) and children treated with periocular corticosteroid injections vs those not treated with periocular corticosteroid injections (HR, 3.23; 95% CI, 0.95 to 11.11). Children treated with methotrexate (MTX) had a longer U–CE interval than children not treated with MTX (HR, 0.29; 95% CI, 0.10 to 0.87).

Conclusions: The risk factor for development of early cataract requiring surgery in children with JIA-associated uveitis is the presence of posterior synechiae at the time of diagnosis of uveitis. However, early treatment with MTX is associated with a mean delay in the development of cataract requiring surgery of 3.5 years.

Introduction

Cataract represents a major complication of uveitis in childhood. It occurs in approximately 35% (range, 20% to 70%) of the cases of juvenile idiopathic arthritis (JIA)-associated uveitis.[1] Cataract can be caused by systemic and local corticosteroid treatment and the intraocular inflammation itself.[2] The risk of cataract formation in JIA-associated uveitis increases when posterior synechiae are present at the initial examination and with treatment with a high dose of systemic corticosteroids.[3] Previously, the visual outcome of cataract surgery in JIA-associated uveitis was poor. Since new surgical techniques have been recommended, the results of cataract extraction (CE) have improved, but surgery in uveitic eyes of children still remains challenging.[4]

The aim of our study was to evaluate which factors accelerate the development of cataract requiring surgery in JIA-associated uveitis. Therefore, clinical and ophthalmologic characteristics and the treatment strategies in children with JIA-associated uveitis were investigated in relation to the interval between the diagnosis of uveitis and the first cataract extraction (U–CE interval).

Methods

We reviewed the medical records of 53 children with JIA-associated uveitis (n=51) or antinuclear antibody (ANA)-positive uveitis without arthritis (n=2) diagnosed before the age of 16 years. These children represent all children with JIA-associated uveitis identified in a complete database search of the FC Donders Institute of Ophthalmology, University Medical Center Utrecht, the Netherlands, from January 1990 through June 2006 (53 of 240 children with uveitis). Our center combines a secondary and a tertiary referral function. Children were referred by the ophthalmologists of secondary referral hospitals or by the pediatric rheumatologists of our medical center. The pediatric rheumatologists referred all children with JIA for uveitis screening according to the criteria of the American Academy of Pediatrics in cases of JIA.[5] The parents of the children gave permission for all the treatment.

In this study, we investigated the clinical data of the first eye that underwent cataract surgery per patient. Cataract surgery to the second eye was not included in this study because possible personal predispositions may interfere with the results. If no CE was performed before the end of follow-up, the data of the first affected eye was included. We recorded the following clinical and ophthalmologic data for each patient: gender, age at diagnosis of uveitis and arthritis, the course

of JIA (arthritis or uveitis as the first manifestation of JIA), ANA status, adherent posterior synechiae and lens opacity at the time of the diagnosis of uveitis, age at first cataract surgery, all intraocular surgeries before CE, and age at last visit to our clinic. Furthermore, we noted all treatment in the first year after the diagnosis of uveitis and before CE or final visit and paid special interest to treatment with methotrexate (MTX), systemic corticosteroids, and periocular corticosteroids. We compared children with the above-mentioned treatment strategies during the first year after the onset of uveitis with children who had never been treated with those drugs. Treatment during the first year was chosen because after more than one year, cataract formation might have developed as a result of other factors. The treatment with corticosteroid drops was not specifically investigated because this treatment method was used in all children.

All intraocular surgeries before CE (n=9) were registered, and all were found to be glaucoma related (trabeculectomy with or without mitomycin C). Cataract surgery was performed if the visual acuity was 20/63 (Snellen) or less. The U–CE interval in the first operated eye was taken as the outcome parameter time until development of cataract requiring surgery. All patients who underwent CE were seen for follow-up. In this study, the follow-up period was defined as the time period between the diagnosis of uveitis and the last ocular examination or CE. The mean follow-up was 3.4 years (range, 0.2 to 14.1 years). Uveitis was classified and categorized according to the criteria of the Standardization of Uveitis Nomenclature Working Group.[6] The diagnosis of JIA was made according to the criteria from the International League against Rheumatism.[7;8] In cases of presumed JIA, the diagnosis was confirmed by a pediatric rheumatologist.

Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS, Inc, Chicago, Illinois, USA). The interquartile range (IQR) was used to show the range between the first and third quartile. The Chi-square test or the Fisher exact test were used to compare categorical data. The independent samples t test was used to compare the means of two groups. The mean U–CE interval was calculated with the Kaplan-Meier survival analysis, which corrects for patients who did not undergo CE before the end of follow-up. The Kaplan-Meier survival analyses were quantified using multivariate Cox proportional hazard analysis (i.e., time-to-event analysis) in which we submitted all variables with a $p<.05$ in univariate analysis.[9] The hazard ratio (HR) was defined to be significant if one did not fall into the 95% confidence interval.

Results

General characteristics. Of all the children investigated in this study, 27 of 53 (51%) underwent CE before the end of follow-up. The mean follow-up of children with and without CE was 3.8 years (IQR, 1.2 to 5.0 years; n=27) and 3.1 years (IQR, 1.0 to 4.1 years; n=26), respectively (p=.593). The mean age at onset of uveitis of children with and without cataract surgery was 4.6 years (IQR, 3.4 to 5.1 years) and 6.2 years (IQR, 3.2 to 8.5 years), respectively (p=.088). The uveitis was chronic and bilateral in all cases, except for two girls who had chronic unilateral uveitis. Data concerning the first manifestation of JIA, the presence of posterior synechiae, and the treatment with MTX and periocular corticosteroid injection(s) in relation to clinical characteristics and treatment strategies are shown in Table 1.

Clinical characteristics in relation to cataract requiring surgery. Children in whom the diagnosis of uveitis was the initial manifestation of JIA (CE, 11/12 [92%]) had a significantly shorter mean U–CE interval than children in whom arthritis preceded uveitis (3.5 years vs CE, 16/41 [39%]; 6.6 years, respectively; Table 2). In the group in which uveitis was the first manifestation of JIA, there were no children treated with MTX in the first year after the diagnosis of uveitis (Table 1). Therefore, adjustment was performed only for the presence of posterior synechiae at the time of diagnosis of uveitis. After adjustment, the difference between arthritis and uveitis as the initial manifestation of JIA did not reach significance (Table 2). If we limit our data to only those patients who had arthritis as the initial manifestation of JIA (n=41), no statistically significant difference was found for the U–CE interval between children treated with MTX during the first year after the diagnosis of uveitis (n=17) and children never treated with MTX (n=15; HR, 0.46; 95% confidence interval [CI], 0.13 to 1.61).

In addition to the course of JIA, we also examined the gender and ANA status of the patients. No statistically significant difference was found for the mean U–CE interval between boys (CE, 11/18 [61%]) and girls (CE, 16/35 [46%]; 4.9 and 5.8 years, respectively; HR, 0.61; 95% CI, 0.26 to 1.41), nor between ANA-positive children (CE, 22/45 [49%]) and ANA-negative children (CE, 4/7 [57%]; 6.2 and 5.9 years, respectively; HR, 1.13; 95% CI, 0.38 to 3.34; Table 2). In one additional child with cataract, the ANA status was unknown.

Ophthalmologic characteristics in relation to cataract requiring surgery. The presence of adherent posterior synechiae at the time of diagnosis of uveitis (CE, 12/15 [80%]) resulted in a significantly shorter mean U–CE interval than when no posterior synechiae were present (CE, 10/33 [30%]; 3.0 vs 8.5 years, respectively; Table 2). After adjustment for treatment with periocular corticosteroid

Table 1. The first manifestation of juvenile idiopathic arthritis, the presence of posterior synechiae and the treatment with methotrexate and periocular corticosteroid injection(s) in children with uveitis associated with juvenile idiopathic arthritis in relation to clinical characteristics and treatment strategies

Children with uveitis associated with JIA (n=53)												
	First manifestation of JIA (n=53)			Posterior synechiae at the time of diagnosis of uveitis (n=48[a])			Treatment with MTX (n=42[b])			Treatment with periocular corticosteroid injection(s) (n=49[c])		
Clinical characteristics	Uveitis (n=12)	Arthritis (n=41)	P value	Yes (n=15)	No (n=33)	P value	During the first year after the diagnosis of uveitis (n=17)	Never treated with MTX (n=25)	P value	During the first year after the diagnosis of uveitis (n=7)	Never (n=42)	P value
Mean age (yrs) at diagnosis of uveitis (median)	4.7 (4.3)	5.6 (4.8)	0.750	5.3 (4.5)	5.5 (5.0)	0.956	6.3 (3.4)	5.3 (4.8)	0.431	5.0 (4.1)	5.7 (4.9)	0.547
Female-to-male ratio	5:7	30:11	0.080	8:7	23:10	0.276	12:5	16:9	0.747	3:4	29:13	0.217
Uveitis as the initial manifestation of JIA	NA	NA	NA	7/15	4/33	0.022	0/17	10/25	0.003	3/7	9/42	0.340
ANA positive[d]	10/12	35/40	0.656	12/15	30/33	0.360	15/17	22/24	1.000	7/7	34/41	0.573
HLA-B27 positive[d]	1/8	2/11	1.000	0/8	3/9	0.206	1/3	0/10	0.231	0/1	3/18	1.000
Presence of posterior synechiae at time of diagnosis of uveitis[e]	7/11	8/37	0.022	NA	NA	NA	4/17	9/21	0.207	5/6	10/38	0.013
Lens opacity at time of diagnosis of uveitis[e]	1/9	2/36	0.497	1/5	2/36	0.330	1/17	2/18	1.000	1/5	2/36	0.330
Treatment with MTX during the first year after the diagnosis of uveitis	0/12	17/41	0.005	4/15	13/33	0.387	NA	NA	NA	2/7	13/42	1.000
Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis	3/12	4/41	0.183	5/15	1/33	0.008	2/17	5/25	0.681	NA	NA	NA
Treatment with systemic corticosteroids during the first year after the diagnosis of uveitis	0/12	1/41	1.000	1/15	0/33	0.313	1/17	0/25	0.405	1/7	0/42	0.143
Glaucoma surgery before CE or the end of follow-up	1/12	8/41	0.665	1/15	8/33	0.239	3/17	1/25	0.286	1/7	5/42	1.000

ANA=antinuclear antibody; CE=cataract extraction; HLA=human leukocyte antigen; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NA=not applicable.
[a]For 5 patients, no information about posterior synechiae at time of diagnosis of uveitis was available
[b]Eleven patients were treated with methotrexate more than one year after the onset of uveitis.
[c]Four patients were treated with periocular corticosteroid injection(s) more than one year after the onset of uveitis.
[d]The ANA and HLA-b27 status was not available for all children.
[e]Data about posterior synechiae and lens opacity at diagnosis of uveitis was not available for all children.

Table 2. Hazard ratios (crude and adjusted) for cataract requiring surgery in children with uveitis associated with juvenile idiopathic arthritis

Variable	Crude HR (95% CI)	Adjustment for	Adjusted HR (95% CI)
Uveitis as the initial manifestation of juvenile idiopathic arthritis (uveitis vs arthritis)	2.44 (1.09 to 5.26)	The presence of posterior synechiae at time of diagnosis of uveitis	1.59 (0.63 to 4.00)
Gender (boys vs girls)	1.64 (0.71 to 3.85)		
ANA status (positive vs negative)	0.88 (0.30 to 2.63)		
Posterior synechiae at time of diagnosis of uveitis (yes vs no)	4.55 (1.82 to 11.11)	Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis and the course of juvenile idiopathic arthritis	3.57 (1.33 to 10.00)
Systemic treatment with methotrexate during the first year after the diagnosis of uveitis (yes vs never)	0.29 (0.10 to 0.87)		
Treatment with periocular corticosteroid injection(s) during the first year after the diagnosis of uveitis (yes vs never)	5.26 (1.89 to 14.29)	The presence of posterior synechiae at time of diagnosis of uveitis	3.23 (0.95 to 11.11)

ANA=antinuclear antibody; CI=confidence interval; HR=hazard ratio.
The HR was defined to be significant if 1 did not fall into the 95% CI.

injections in the first year after the diagnosis of uveitis and for the course of JIA, the difference between the two groups remained significant (Table 1 and Table 2). In five children, no information about posterior synechiae at time of diagnosis of uveitis was available.

Three children were observed with lens opacity at the time of diagnosis of uveitis. Because of this small number, the relation between lens opacity and the development of cataract requiring surgery was not evaluated.

Children with CE who previously had undergone glaucoma surgery (n=7) and children without previous glaucoma surgery (n=20) had a mean U–CE interval of 5.4 and 3.2 years, respectively. The mean period between the diagnosis of uveitis and glaucoma surgery was 4.2 years, and the mean period between glaucoma surgery and CE was 0.8 years. Between these two groups, no significant differences were found concerning treatment in the first year after the diagnosis of uveitis with MTX and periocular corticosteroid injections (p=1.000 and p=1.000, respectively).

Systemic treatment with MTX. Children who started MTX treatment during the first year after the diagnosis of uveitis (CE, 5/17 [29%]) had a significantly longer mean U–CE interval than children who were never treated with MTX (CE, 16/25 [64%]; 7.0 vs 3.5 years, respectively; Table 2). In 11 patients, MTX was started more than one year after the onset of uveitis. The indication for starting MTX treatment was uveitis not responding to topical corticosteroid treatment in five children and arthritis in 12 children. In the group treated with MTX during the first year after the diagnosis of uveitis, significantly fewer children had uveitis as the initial manifestation of JIA than children never treated with MTX (p=.003; Table 1). Adjustment could not be performed for the course of JIA, because there were no children with uveitis as the initial manifestation of JIA in the MTX-treated group. If we limited our data to only those patients who were never treated with MTX (n = 25), then children with uveitis as the initial manifestation of JIA (CE, 9/10 [90%] after 1.8 years) had a significantly shorter U–CE interval than children who had arthritis as the first manifestation (CE, 7/15 [47%] after 5.1 years) with an HR of 3.13 (95% CI, 1.08 to 9.09).

Systemic treatment with corticosteroids. The relation between systemic corticosteroid treatment and the development of cataract could not be evaluated because there was only one child who had started systemic corticosteroid treatment during the first year after the diagnosis of uveitis.

Treatment with periocular corticosteroid injections. Seven children were treated with periocular corticosteroid injection(s) in the first year after the diagnosis of uveitis. Of these, five children received one injection (including one child not operated on for cataract) and one child received five injections, and for one child, the number of injections in the first year after the diagnosis of uveitis was unclear. These children (CE, 6/7 [86%]) had a significantly shorter U–CE interval than children never treated with periocular corticosteroid injections (CE, 17/42 [40%]; 1.8 vs 7.1 years, respectively; Table 2). Adjusting for the presence of posterior synechiae at the time of diagnosis of uveitis did not reach significance, but there was still a trend toward earlier cataract formation in children treated with corticosteroid injections (Table 1 and Table 2). Four patients were treated with periocular corticosteroid injection(s) more than one year after the onset of uveitis.

Discussion

This study demonstrates that the presence of adherent posterior synechiae at the time of diagnosis of uveitis is strongly associated with the early development of cataract requiring surgery in JIA-associated uveitis and that treatment with MTX in the first year after the diagnosis of uveitis is associated with a delay in cataract surgery. Previous studies have demonstrated that the presence of posterior synechiae at the time of diagnosis of uveitis is associated with a poor visual prognosis in JIA-associated uveitis.[3] Because of the association with poor visual outcome, detection of uveitis before the formation of posterior synechiae development is recommended. Therefore, screening of uveitis should occur shortly after the onset of arthritis. Chia and associates have advocated for more intensive screening for uveitis in the first year after the diagnosis of JIA in the hope of reducing the rate of complications.[10] In concordance with Chia and associates, we believe that more intensive screening in the early phase of JIA may result in less frequent development of posterior synechiae and therefore less early development of cataract. When uveitis is diagnosed, prompt, careful follow-up should ensue, especially in cases where posterior synechiae already are present. However, in children in whom uveitis precedes arthritis, early detection of uveitis is not possible because these children have the intraocular inflammation without notice. Furthermore, one can speculate that the presence of posterior synechiae may be an indication for early treatment with MTX because this drug was associated with a delay proceeding to cataract surgery. In this study, the presence of posterior synechiae was equal in both groups treated with MTX in the first year and in the group never treated with MTX.

In addition to the presence of posterior synechiae, treatment with periocular corticosteroid injections in the first year after the diagnosis of uveitis showed a trend, although not a significant one, toward a more rapid cataract requiring surgery development. In our series, we do not know the duration of uveitis before the diagnosis. Therefore, we cannot determine whether this is of influence on the early development of cataract requiring surgery. Whether the differences found for children with posterior synechiae and children treated with periocular corticosteroid injections were caused by a more intense uveitis or whether this difference is removed after adjustment for the unknown duration of uveitis before diagnosis is unclear.

We could not investigate the effect of treatment with systemic corticosteroids in our series because there was only one child who had received this treatment in the first year. However, literature reports that systemic corticosteroids enhance cataract formation.[3]

The only modifiable factor that may be associated with a delay in the development of cataract requiring surgery was early treatment with MTX. If MTX treatment was started during the first year after the diagnosis of uveitis, the development of cataract was not accelerated, but rather was postponed by a mean of 3.5 years. Because cataract development in JIA-associated uveitis is caused by various factors, it is difficult to determine the specific importance of a single factor. Unfortunately, adjustment for the course of JIA (first manifestation of JIA) was not possible, because there were no children with JIA as the initial manifestation of JIA in the group treated with MTX. Referral bias cannot be excluded because our uveitis clinic is a combined secondary and tertiary center. However, patients with uveitis as well as arthritis as the initial manifestation of JIA were referred by their ophthalmologist. A possible explanation for the lack of children with uveitis as the initial manifestation of JIA may be that presently, MTX is not (yet) administered as the first treatment of choice for uveitis when there are no signs of arthritis. Treatment with topical corticosteroids initially is indicated, and only severe cases are treated with MTX. So if the cases who received MTX have a higher baseline risk of developing cataract requiring surgery, the benefit of MTX in delaying cataract surgery may have been reduced artificially, and the benefit may be even greater than what we observed. However, the delay in cataract surgery is still a remarkable observation, because the other treatment strategies were associated with a shortening of the U–CE interval. A delay in cataract formation is very favorable for several reasons. It is well known that CE in children is complicated because of anatomic and functional characteristics, which include the small globe size, increased tissue reactivity, lower scleral rigidity, changing axial length, and the risk of amblyopia.[11;12] Furthermore, with a delay in cataract formation, it will be easier to treat secondary posterior capsule opacification, to measure axial length and keratometry, and to perform capsulotomies. If cataract development can be postponed, the visual prognosis may improve, especially in young children in whom the period in which management to prevent amblyopia is necessary will be shortened. The protective mechanism responsible for the delay of development of cataract requiring surgery in children treated with MTX may include better control of the intraocular inflammation with possibly fewer flare-ups during the course of the disease. Another explanation may be that treatment with MTX diminishes the need for treatment with topical or systemic corticosteroids. However, both hypotheses need further investigation.

A limitation of this study is the relatively small number of patients available for statistical analysis, especially of some subgroups. Because of these small numbers, no analysis could be carried out on lens opacity and systemic corticosteroids in

relation to the development of cataract requiring surgery. Furthermore, no patients were included who had been treated with MTX and who had uveitis as the initial manifestation of JIA, so adjustment for the course of JIA could not be performed in this subgroup. Another limitation is the possible bias resulting from the time of cataract surgery. All children had a visual acuity of 20/63 (Snellen) or less before CE. However, the final decision to perform cataract surgery is not based solely on visual acuity, but on a combination of visual acuity, the risk of amblyopia, clinical findings, and the symptoms and preferences of patients and parents. So the different time schedules adopted for performing CE may well have influenced the results.

What is positive about this study is that it included only children with JIA-associated uveitis, which means it is based on a homogeneous population. Furthermore, all the children were seen in the same institute, and the different analyses were all performed on one relatively large study group with a relatively long median follow-up of 3.4 years. For further study, it may be interesting to compare early treatment (during the first year after the diagnosis of uveitis), late treatment (treatment after more than one year after the onset of uveitis), and no treatment with MTX, periocular corticosteroid injections, or both in a large patient series.

In conclusion, development of cataract requiring surgery in JIA-associated uveitis is caused by various factors. The presence of adherent posterior synechiae at the time of diagnosis of uveitis is strongly associated with the early development of cataract requiring surgery in children with JIA-associated uveitis. This is in contrast with early treatment with MTX, which is associated with a delay in the development of cataract requiring surgery. So the beneficial effect of early treatment with MTX on the development of cataract requiring surgery may be expected in cases with posterior synechiae. These observations are of value for ophthalmologists treating chronic severe uveitis in children with JIA.

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Chapter 5

Long term ocular complications in aphakic versus pseudophakic eyes of children with juvenile idiopathic arthritis-associated uveitis

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Abstract

Purpose: To evaluate the long-term follow-up of aphakic and pseudophakic eyes of children with juvenile idiopathic arthritis (JIA)-associated uveitis and of pseudophakic eyes of children with uveitis not associated with JIA (non-JIA) with a special interest in whether intraocular lens (IOL) implantation increases the risk of developing secondary glaucoma (SG), cystoid macular edema (CME), optic disc swelling (DS), perilenticular membrane formation or hypotony.

Design: Retrospective cohort study.

Methods: Forty-eight eyes of 29 children with JIA-associated uveitis and 17 eyes of 14 children with non-JIA associated uveitis and cataract extraction before the age of 16 years between January 1990 and March 2007 were enrolled in this multicenter study. The medical records of all patients included were evaluated. Main outcome measures were long-term postsurgical complications and visual acuity.

Results: The number of complications after cataract extraction; new onset of ocular hypertension (OHT) and SG, CME, DS and hypotony did not differ between aphakic JIA and pseudophakic JIA eyes and nor between pseudophakic JIA and pseudophakic non-JIA eyes. Moreover, no hypotony, perilenticular membranes and phthisis were encountered in the pseudophakic JIA group. Better visual acuity was observed in pseudophakic than in aphakic JIA eyes until the 7-year follow-up.

Conclusions: With maximum control of inflammation and intensive follow-up, the implantation of an IOL in children with JIA-associated uveitis is not associated with an increased risk of OHT, SG, CME or DS and showed better visual results up to 7 years after cataract extraction than aphakic JIA eyes.

Introduction

Cataract is a frequent complication of pediatric uveitis and involves about half of the children affected.[1;2] The choice of an appropriate surgical technique is crucial for the visual outcome after cataract extraction since previously, eyes frequently became hypotonic.[3-5] In children with uveitis, handling the pre- and postsurgical inflammation and dealing with uveitis-related complications make cataract surgery challenging. The presence of posterior synechiae, pupillary sclerosis and pupillary membrane formation may limit the surgical access.[6] Several studies reveal favorable surgical and visual outcomes after the implantation of an intraocular lens (IOL) in selected cases of JIA-associated uveitis.[7-11] Although the advantages of IOL implantation are obvious for visual rehabilitation and amblyopia prevention, in JIA-associated uveitis it has frequently been associated with poor visual outcome as a consequence of complications including hypotony, cyclitic or fibrous membrane formation, IOL deposits, macular edema and posterior synechiae.[12;13] In some cases, progressive intraocular damage from intractable uveitis, perilenticular (cocoon) or ciliary membranes formation resulted in the decision to explant the IOL.[14] The role of IOL implantation in the development of secondary glaucoma (SG), cystoid macular edema (CME), optic disc swelling (DS) and hypotony in pediatric uveitis is unknown. The purpose of our study was to evaluate the long-term follow-up of aphakic and pseudophakic eyes of children with juvenile idiopathic arthritis (JIA)-associated uveitis with a special interest in whether IOL implantation increases the risk of developing SG, CME, DS, perilenticular membrane formation or hypotony.

Materials and methods

A retrospective review of the medical records of children with uveitis who underwent cataract extraction at the Department of Ophthalmology, University Medical Center Utrecht, the Netherlands and at the Department of Ophthalmology, University Medical Center, Groningen, the Netherlands between January 1990 and March 2007 was performed. Both centers combine a secondary and a tertiary referral function. The inclusion criteria were onset of uveitis and cataract extraction before the age of 16 years with a minimum follow-up after cataract extraction of 1 year. Exclusion criteria were cataract extraction after the age of 16, follow-up of less than 1 year, incomplete data, phacogenic uveitis, traumatic cataract and aphakic eyes of children with uveitis not associated with JIA (non-JIA). Included in this study were 48 eyes (29 children) with JIA-associated uveitis of whom 29

eyes were pseudophakic (polymethylmethacrylaat n=5, acrylic n=24) and 19 eyes aphakic after cataract extraction plus 17 eyes (14 children) with non-JIA uveitis (Fuchs heterochromic iridocyclitis n=2 and uveitis of unknown etiology n=12) which were all pseudophakic (polymethylmethacrylaat n=5, acrylic n=12).
Cataract surgery was performed if the visual acuity was 20/50 (Snellen) or less or in the presence of interfering lens opacities. Before ocular surgery we attempted to eliminate the intraocular inflammation for a minimum of three months. The date of the first and last included eye operated on was April 1991 and March 2007 for the pseudophakic JIA group and March 1990 and February 2002 for the aphakic JIA group respectively. During surgery, an anterior vitrectomy was performed in 23 (79%) pseudophakic JIA eyes, all (100%) aphakic JIA eyes and 6 (35%) pseudophakic non-JIA eyes.
We recorded the following clinical data for each patient: gender, age at diagnosis of uveitis, age at cataract extraction, intraocular procedures, pre-operative ocular hypertension (OHT) or SG and whether an IOL was implanted or not. Postoperatively, we recorded the VA, ocular complications, and treatment strategies at set time points. Measured ocular complications were new onset OHT or SG, CME, DS, perilenticular membranes and phthisis. Diagnosis of uveitis was based on the criteria of the Standardization of Uveitis Nomenclature (SUN) Workshop.[15] The diagnosis of JIA was made according to the criteria from the International League against Rheumatism (ILAR) and was confirmed by a pediatric rheumatologist.[16-18] The intraocular pressure was measured by applanation tonometry, but if this was not possible, noncontact tonometry, the Tono-Pen or the Icare tonometer were used. Secondary glaucoma and OHT were defined as previously described.[19] For the purpose of this study, ocular hypotony was documented to be present when IOP was lower than 5mmHg for longer than 3 months in the absence of glaucoma surgery. Patients' Snellen visual acuity was converted to logMAR (log of the minimal angle of resolution) units for statistical assessment and converted back to Snellen equivalents for data presentation in Table 5. Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS Inc., Chicago, IL). The Pearson chi-square test or the Fisher exact test were used to compare possible associations between categorical variables. To compare means we used the Mann-Whitney test or the Kruskal-Wallis test. P values of $<.05$ were considered to be statistically significant.

Results

General characteristics. The clinical data of all eyes before cataract extraction are shown in Table 1.

There were some differences in presurgical characteristics between the groups. The pseudophakic JIA group had a significantly longer time interval between the diagnosis of uveitis and cataract extraction (3.0 years versus 1.6 years; p=.012), had more OHT (66% versus 26%; p=.017) and SG (52% versus 11%; p=.005), more intraocular surgeries (52% versus 0%; p<.001) and significantly more children were treated with MTX (59% versus 16%; p=.006, Table 1) than the aphakic JIA group. The pseudophakic non-JIA group was significantly older at the time of diagnosis of uveitis (9.6 years versus 4.0 years, p<.001) and at the time of cataract extraction (12.0 years versus 7.6 years, p=.002) than the pseudophakic JIA group (Table 1). No differences in the preoperative treatment with topical, periocular or

Table 1. Clinical characteristics before cataract extraction of aphakic JIA, pseudophakic JIA and pseudophakic non-JIA eyes of children with uveitis

	Aphakic JIA =group 1	Pseudophakic JIA =group 2	Pseudophakic non-JIA =group 3	P value	Group 1 versus group 2 P value	Group 2 versus group 3 P value
No. of eyes	19	29	17			
Female-to-male ratio	8:11	21:8	10:7	0.109		
Median age (yrs) at the diagnosis of uveitis (range)	4.4 (2.8-7.4)	4.0 (1.9-9.2)	9.6 (3.4-14.6)	<0.001	0.268	<0.001
Median age (yrs) at cataract extraction (range)	6.3 (4.5-12.3)	7.6 (3.9-14.6)	12.0 (4.5-15.2)	0.001	0.370	0.002
Median time interval (yrs) between the diagnosis of uveitis and cataract extraction (range)	1.6 (0.8-8.5)	3.0 (0.2-10.6)	1.8 (0.0-6.7)	0.029	0.012	0.067
OHT before cataract extraction (%)	5 (26)	19 (66)	11 (65)	0.020	0.017	1.000
SG before cataract extraction (%)	2 (11)	15 (52)	7 (41)	0.010	0.005	0.552
Methotrexate (%)	3 (16)	17 (59)	6 (35)	0.011	0.006	0.221
Intraocular surgery before cataract extraction (%)	0 (0)	15[a] (52)	5[b] (29)	<0.001	<0.001	0.219

JIA=juvenile idiopathic arthritis; No.=number; OHT=ocular hypertension; SG=secondary glaucoma.
[a]Trabeculectomy n=12, Baerveldt n=1, combined Baerveldt implantation with cataract extraction n=2.
[b]Trabeculectomy n=5.

systemic corticosteroids or in the adjuvant perioperative treatment with systemic or periocular corticosteroids, to prevent postoperative inflammation, were found between the three groups.

Aphakic JIA versus pseudophakic JIA eyes. No significant differences in complications including new onset of OHT and SG, CME, DS and hypotony were found between aphakic JIA and pseudophakic JIA eyes during the first 10 years after cataract extraction (Tables 2-4). The highest percentages of CME and the only cases of hypotony were observed in the aphakic JIA eyes (Table 4). The VA of pseudophakic JIA eyes was significantly better up to and including 7 years after cataract extraction compared to the aphakic group (Table 5). In this study, no eyes with a cocoon formation round the IOL were found. Phthisis was found in only 1 aphakic JIA eye, which occurred after glaucoma drainage implant 3 years after cataract extraction. An unexplained episode of DS was found in only 2 eyes (15%) of the pseudophakic JIA group. In both eyes, the DS disappeared after several weeks.

Pseudophakic JIA eyes versus pseudophakic non-JIA eyes. The number of complications between pseudophakic JIA eyes and pseudophakic non-JIA eyes did not differ during the first 3 years after cataract extraction (Table 2-4). However, the highest percentage of CME was found in the non-JIA group (Table 4). One year after cataract extraction, the VA was significantly better in the pseudophakic JIA group than in the pseudophakic non-JIA group (20/20 versus 20/30, p=.031; Table 5).

Discussion

This study demonstrates that the implantation of an IOL in children with JIA-associated uveitis does not increase the risk of developing OHT, SG, CME and DS during 10 years of follow-up. Moreover, no hypotony, perilenticular membranes and phthisis were encountered in the pseudophakic JIA group. In our study, the VA was better in the pseudophakic JIA group than in the aphakic JIA group. This supports the results of recent studies in which the implantation of an IOL in selected cases of JIA-associated uveitis was associated with good visual results.[7-11] Asrani *et al* found lower incidences of open-angle glaucoma in pseudophakic eyes of children with congenital or developmental cataract without ocular inflammation compared with aphakic eyes.[20] We found similar percentages of SG with or without the implantation of an IOL in children with uveitis. This difference might be explained by the fact that our study concerns SG due to inflammatory eye disease. Our findings indicate that the implantation of an IOL in children with

Table 2. New onset of ocular hypertension after cataract extraction in aphakic JIA, pseudophakic JIA and pseudophakic non-JIA eyes of children with uveitis

	Aphakic JIA =group 1	Pseudophakic JIA =group 2	Pseudophakic non-JIA =group 3	P value
No. of eyes[a]	14	10	6	
New onset of OHT after cataract extraction				
3 mos after cataract extraction (%)	2/14 (14)	1/10 (10)	1/6 (17)	1.000
1 yr after cataract extraction (%)	3/14 (21)	3/10 (30)	2/6 (33)	0.761
3 yrs after cataract extraction (%)	7/14 (50)	1/6 (17)	1/3 (33)	0.577
5 yrs after cataract extraction (%)	10/14 (71)	1/5 (20)	1/1 (100)	0.109
7 yrs after cataract extraction (%)	9/11 (82)	2/4 (50)	1/1 (100)	0.637
10 yrs after cataract extraction (%)	7/9 (78)	2/3 (67)	NA	1.000

JIA=juvenile idiopathic arthritis; NA=not applicable; No.=number; OHT=ocular hypertension; SG=secondary glaucoma.
[a]Eyes with ocular hypertension prior to cataract extraction were excluded.

Table 3. New onset of secondary glaucoma after cataract extraction in aphakic JIA, pseudophakic JIA and pseudophakic non-JIA eyes of children with uveitis

	Aphakic JIA =group 1	Pseudophakic JIA =group 2	Pseudophakic non-JIA =group 3	P value
No. of eyes[a]	17	14	10	
OHT before cataract extraction (%)	3 (18)	4 (29)	4 (40)	0.494
New onset of SG after cataract extraction				
3 mos after cataract extraction (%)	1/17 (6)	1/14 (7)	0/10 (0)	1.000
1 yr after cataract extraction (%)	1/17 (6)	1/14 (7)	0/10 (0)	1.000
3 yrs after cataract extraction (%)	4/17 (24)	3/9 (33)	1/3 (33)	0.844
5 yrs after cataract extraction (%)	7/17 (41)	2/6 (33)	1/1 (100)	0.616
7 yrs after cataract extraction (%)	10/13 (77)	1/4 (24)	1/1 (100)	0.083
10 yrs after cataract extraction (%)	7/9 (78)	1/3 (33)	NA	0.236

JIA=juvenile idiopathic arthritis; NA=not applicable; No.=number; OHT=ocular hypertension; SG=secondary glaucoma.
[a] Eyes with secondary glaucoma prior to cataract extraction were excluded.

JIA-associated uveitis is neither protective nor a risk factor for the development of SG. Whether IOL implantation in other uveitis entities influences the development of SG cannot be concluded from our results, since we only studied pseudophakic non-JIA eyes and no aphakic non-JIA eyes of children with uveitis. Another

Table 4. Cystoid macular edema, disc swelling and hypotony after cataract extraction in aphakic JIA, pseudophakic JIA and pseudophakic non-JIA eyes of children with uveitis

	Aphakic JIA =group 1	Pseudophakic JIA =group 2	Pseudophakic non-JIA =group 3	P value
First yr after cataract extraction[a]				
CME (%)	3/19 (16)	1/29 (3)	4/17 (24)	0.100
DS (%)	0/19 (0)	0/29 (0)	2/17 (12)	0.065
Hypotony (%)	1/19 (5)	0/29 (0)	0/17 (0)	0.554
First 3 yrs after cataract extraction				
CME (%)	7/19 (37)	2/20 (10)	2/6 (33)	0.124
DS (%)	0/19 (0)	2/20 (10)	0/6 (0)	0.616
Hypotony (%)	2/19 (11)	0/20 (0)	0/6 (0)	0.424
First 5 yrs after cataract extraction				
CME (%)	7/19 (37)	1/13 (8)	0/2 (0)	0.142
DS (%)	0/19 (0)	2/13 (15)	0/2 (0)	0.255
Hypotony (%)	2/19 (11)	0/13 (0)	0/2 (0)	0.560
First 7 yrs after cataract extraction				
CME (%)	8/14 (57)	1/4 (25)	0/1 (0)	0.433
DS (%)	0/14 (0)	1/4 (25)	0/1 (0)	0.263
Hypotony (%)	2/14 (14)	0/4 (0)	0/1 (0)	1.000
First 10 yrs after cataract extraction				
CME (%)	6/10 (60)	0/3 (0)	NA	0.192
DS (%)	0/10 (0)	0/3 (0)	NA	NA
Hypotony (%)	1/10 (10)	0/3 (0)	NA	1.000

CME=cystoid macular edema; DS=disc swelling; JIA=juvenile idiopathic arthritis; NA=not applicable.
[a]Only cystoid macular edema and disc swelling after the first 3 months after cataract extraction were scored positive. Hypotony was defined as an IOP of <5mmHg for more than 3 months in the absence of glaucoma surgery after cataract extraction.

discrepancy with the study of Asrani *et al* is that their aphakic patients were younger at the time of cataract surgery than their pseudophakic patients. In our study, the age at time of cataract extraction was similar for both the pseudophakic and aphakic JIA patients.

Though not significant, the highest percentages of CME in the JIA population were found in aphakic JIA eyes. Five years after cataract extraction, almost 40% of the aphakic JIA eyes had suffered from one or more episodes of CME compared to 8% in the pseudophakic JIA group. Possible explanations for the development of CME in the aphakic group might be intermittent vitreous prolapses in the anterior

Table 5. Long-term follow-up of the visual acuity after cataract extraction in aphakic JIA, pseudophakic JIA and pseudophakic non-JIA eyes of children with uveitis

	Aphakic JIA =group 1	Pseudophakic JIA =group 2	Pseudophakic non-JIA =group 3	P value	Group1 versus group 2 P value	Group 2 versus group 3 P value
VA before cataract extraction						
Median[a]	20/400	20/100	20/125	0.792		
≤20/200	11 (58)	11 (38)	7 (41)			
20/200 – 20/40	8 (42)	16 (55)	8 (47)			
≥20/40	0 (0)	2 (7)	2 (12)			
VA 3 mos after cataract extraction						
Median[a]	20/32	20/25	20/32	0.190		
≤20/200	2 (11)	2 (7)	2 (12)			
20/200 – 20/40	4 (21)	3 (10)	2 (12)			
≥20/40	13 (68)	24 (83)	13 (76)			
VA 1 yr after cataract extraction						
Median[a]	20/40	20/20	20/30	<0.001	<0.001	0.031
≤20/200	2 (11)	1 (3)	1 (6)			
20/200 – 20/40	4 (21)	3 (10)	2 (12)			
≥20/40	13 (68)	25 (86)	14 (82)			
VA 3 yrs after cataract extraction			20/32			
Median[a]	20/32[b]	20/20	20/32	0.004	0.001	0.196
≤20/200	2 (11)	1 (5)	1 (17)			
20/200 – 20/40	5 (26)	0 (0)	2 (33)			
≥20/40	12 (63)	19 (95)	3 (50)			
VA 5 yrs after cataract extraction						
Median[a]	20/30[b]	20/20	20/20[b]	0.012	0.005	1.000
≤20/200	4 (21)	1 (8)	1 (50)			
20/200 – 20/40	3 (16)	0 (0)	0 (0)			
≥20/40	12 (63)	12 (92)	1 (50)			
VA 7 yrs after cataract extraction						
Median[a]	20/50[b]	20/25	NA[b]	NA	0.012	NA
≤20/200	4 (29)	0 (0)	1 (100)			
20/200 – 20/40	3 (21)	0 (0)	0 (0)			
≥20/40	7 (50)	4 (100)	0 (0)			
VA 10 yrs after cataract extraction						
Median[a]	20/50[b]	20/25	NA	NA	0.217	NA
≤20/200	4 (40)	0 (0)	(0)			
20/200 – 20/40	2 (20)	0 (0)	(0)			
≥20/40	4 (40)	3 (100)	(0)			

JIA=juvenile idiopathic arthritis; NA=not applicable; VA=visual acuity.
[a]For computing the median visual acuity all Snellen values were converted to the logMAR equivalent and afterwards the logMAR equivalent was converted back to the Snellen value.
[b]One patient had visual acuity of perception of light and was therefore excluded from the calculation of the median visual acuity.

chamber due to the absence of an anatomic barrier between the anterior chamber and the vitreous cavity, and the lack of a barrier to immune mediators between the anterior and posterior segment of the eye. Whether the surgical technique of cataract extraction combined with anterior vitrectomy was of influence on the development of CME cannot be concluded from our study population because the number of patients with CME was too small. However, the systemic treatment might have been of influence in the prevention of CME since the aphakic group was less frequently treated with MTX and might have had less profound control of inflammation. In previous articles, a wide range of percentages of CME (7%-42%) were reported in a general JIA-associated uveitis population regardless of the phakic, aphakic and pseudophakic state of the eyes.[21-23] We observed higher percentages (not significant) of CME in the pseudophakic eyes of the non-JIA patients than in the pseudophakic eyes of the JIA patients which might indicate that patients with non-JIA uveitis might be more prone to the development of CME than patients with JIA-associated uveitis. The better VA after 1 year of follow-up in the pseudophakic JIA eyes than in the pseudophakic non-JIA eyes might be explained by the lower percentage of CME in the first group (3% versus 24%, respectively) and/or by a more aggressive treatment of the intraocular inflammation.

The limitations of this study include the limited number of patients in particular at longer follow-up times. In addition, prior to surgery, the aphakic and pseudophakic JIA eyes differed in the time interval between the diagnosis of uveitis and of cataract extraction, the pre-existence of OHT and SG, the number of previous intraocular surgeries and the treatment with MTX. A longer history of uveitis and more patients with previous glaucoma surgery makes the pseudophakic JIA group a more complicated one than the aphakic JIA group. In eyes with uveitis, surgical success is strongly dependent on the pre- and postoperative treatment and long-term perioperative control of inflammation is necessary for a favorable outcome. Experts advise that the intraocular inflammation should be quiescent for a minimum of 3 months before surgery.[25] To achieve this, most of our patients were pre- and postsurgically treated with systemic and/or periocular corticosteroids and all patients were frequently evaluated during the first days after surgery and later on a regular basis.

In conclusion, in our study with maximum control of inflammation and intensive follow-up, IOL implantation in children with JIA-associated uveitis was not associated with an increased risk of OHT, SG, CME or DS and shows better visual results up to 7 years after cataract extraction than aphakic eyes of children with JIA-associated uveitis.

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Chapter 6

Cytokines, chemokines and soluble adhesion molecules in aqueous humor of children with uveitis

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Abstract

Uveitis in childhood is a visual threatening disease with a complication rate of more than 75%. Despite extensive research, the etiology of uveitis is still unclear although the general opinion is now that uveitis is a T-cell mediated disease. The purpose of this study was to investigate the profile of cytokines, chemotactic cytokines (chemokines) and soluble adhesion molecules in the aqueous humor (AqH) of children with uveitis in order to identify the factors that control the immune response in the eye. In this clinical laboratory investigation we analyzed, with a multiplex immunoassay, 16 immune mediators in the AqH of 25 children with uveitis and 6 children without uveitis. Increased levels of interleukin-2 (IL-2), IL-6, IL-10, IL-13, IL-18, interferon-γ, tumor necrosis factor-α, soluble intercellular adhesion molecule-1, RANTES, IL-8 and interferon-inducible 10-kDa protein were found in the AqH of children with uveitis compared with controls. No significant differences were found for IL-1β, IL-4, IL-12 p-70, soluble vascular cell adhesion molecule 1 and Eotaxin. Lower levels of IL-10 and IL-8 were found in quiet stage uveitis (surgical) samples compared with active uveitis (diagnostic) samples and in samples of patients treated with methotrexate (MTX) compared with samples of patients not treated with MTX. Lower levels of IL-10 were as well found in samples taken during the first 3 months after the diagnosis of uveitis than samples taken later during the disease process. No significant differences were found between patients treated with or without topical or systemic (perioperative and long term) corticosteroids. In conclusion, in children with uveitis, multiple intraocular cytokines, chemokines and soluble adhesion molecules are increased in the AqH regardless of active or inactive inflammation. Whether the IL-8 and IL-10 levels in AqH of children with uveitis are correlated with uveitis activity, early or late phase of the course of the disease and systemic treatment with MTX needs further investigation in a bigger study population.

Introduction

Uveitis in childhood is a visual threatening disease with a complication rate of more than 75%.[1] Despite extensive research, the etiology of uveitis is still unclear although the general opinion is now that uveitis is a T-cell mediated disease.[2] Several studies have shown that several cytokine levels are elevated in the aqueous humor (AqH) of patients with uveitis.[3;4] However, these studies are based on adult study populations but the immune mediator profile in AqH of childhood uveitis is unknown. Uveitis in childhood differs in several aspects of that in adults. The clinical presentation, underlying cause and complications of uveitis differs between children and adults.[1;5-8] Whether these differences reflex the cytokine profile in AqH is not yet clear. The purpose of this study was to investigate the profile of cytokines, chemotactic cytokines (chemokines) and soluble adhesion molecules in the AqH of children with uveitis in order to identify the factors that control the immune response in the eye of this young population.

Materials and methods

Patients. This research followed the tenets of the Declaration of Helsinki and was approved by our institutional review board. Written informed consent was obtained from each child and/or parent after explanation of the nature of the study. AqH samples were collected as prescribed previously, stored immediately at −80 °C in sterile screw-cap tubes and thawed directly before analysis within 4 years of collection.[9] This technique is to preserve the sample for analysis without degradation. AqH samples of 25 children with uveitis under the age of 16 were used. These samples were obtained between 2002 and 2005 during surgery for cataract (n=8) or glaucoma (n=8). In the perioperative period patients were treated with systemic corticosteroids (1 mg/kg) starting 1 day to 1 week before surgery (n=9), long-term systemic corticosteroids (n=3) or no systemic corticosteroids (n=4). The remaining 9 samples were collected for diagnostic purposes. These 9 samples were analyzed for herpes simplex virus, varicella zoster virus and *Toxoplasma gondii* antibodies and DNA by PCR.[10] The clinical data of all patients are shown in Table 1. AqH samples of 6 children under the age of 16, who had an operation for congenital cataract (n=3), glaucoma not associated with uveitis (n=2) or lens subluxation due to Marfan's syndrome (n=1), were collected as controls. In 6 children with uveitis (nos. 3, 7, 8, 17, 18 and 25), more than one sample was available of the same eye. We compared in these 6 pairs of samples the levels of cytokines, chemokines and soluble adhesion molecules before and after surgery. We recorded the following clinical data for each patient: age at diagnosis of uveitis,

age at the time of sample collection, localization and course of uveitis (acute or chronic), underlying systemic disease and (systemic) treatment at the time of sample collection (Table 1).

Immunoassay. We analyzed the AqH samples in a multiplex immunoassay as described previously.[11] In each 50-μl sample, we analyzed 16 mediators; interleukin-1β (IL-1β), IL-2, IL-4, IL-6, IL-10, IL-12 p-70, IL-13, IL-18, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), soluble intercellular adhesion molecule 1 (sICAM-1; CD54), soluble vascular cell adhesion molecule 1 (sVCAM-1; CD106), RANTES (Regulated on Activation, Normal T-cell Expressed, and Secreted; CCL5), Eotaxin (CCL11), IL-8 (CXCL8) and interferon-inducible 10-kDa protein (IP-10; CXCL10). Concentrations above or below the detection limit were given as the highest or lowest detectable value. For statistical analysis concentrations below the detection limit were converted to a value of 0.5 × the lowest point of the calibration curve.

Statistical analysis. Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS Inc., Chicago, IL). The Kruskal–Wallis and the Mann–Whitney *U*-tests were used to compare the means of the (non-parametric) different groups. The Pearson Chi-square test or Fisher's exact test was used to compare possible associations between categorical variables where appropriate. We used the Wilcoxon Signed Rank test to compare paired samples. P values of $<.05$ were considered to be statistically significant.

Results

Aqueous humor was collected from 25 children with uveitis associated with juvenile idiopathic arthritis (JIA; n=11), herpes virus infection (n=1), Fuchs' heterochromic cyclitis (n=1), HLA-B27 (n=2), Devic's neuromyelitis optica (NMO; n=1) or of unknown etiology (n=9, Table 1). The child with a herpes virus infection had a keratouveitis and the diagnosis was confirmed by a positive PCR for varicella-zoster virus in AqH. Both patients with HLA-B27 positive uveitis had acute alternating anterior uveitis. The mean age at sample collection was 9.6 years (range 5.2–14.8 years) for children with uveitis and 3.3 years (range 0.2–9.5 years, p=.002) for the control patients. The mean duration of uveitis till sampling was 2.3 years (median: 1.4 years, range: 0–9 years).

Significantly higher levels of IL-2, IL-6, IL-10, IL-13, IL-18, IFN-γ, TNF-α, sICAM-1, RANTES, IL-8 and IP-10 were found in children with uveitis than in children without uveitis (Table 2). The levels of IL-1β, IL-4, IL-12 p-70, sVCAM-1 and Eotaxin did not significantly differ in AqH of uveitis compared with controls (Table 2). No significant differences were found between anterior (n=16) and intermediate (n=5)

Table 1. Clinical data of all uveitis patients

No.	Gender	Age at diagnosis of uveitis (yrs)	Age at aqueous humor sample collection (yrs)	Localization of uveitis	Underlying cause of uveitis	Course of uveitis	Sample type	Sample taken during the first 3 months after the diagnosis of uveitis	Topical cortico-steroids	Systemic cortico-steroids	MTX (mg/ week)
1	F	3.9	12.8	Anterior	JIA	Chronic	Surgical[b]	No	Yes	Perioperative	10
2	M	4.1	5.5	Anterior	JIA	Chronic	Surgical[b]	No	Yes	No	7.5
3[a]	F	4.5	12.8	Anterior	JIA	Chronic	Surgical[b]	No	Yes	No	10
							Surgical[c]	No	No	Perioperative	10
4	F	3.9	5.6	Anterior	JIA	Chronic	Surgical[b]	No	Yes	Perioperative	0
5	F	1.9	5.2	Anterior	JIA	Chronic	Surgical[b]	No	Yes	Perioperative	20
6	F	9.4	11.4	Anterior	JIA	Chronic	Surgical[c]	No	Yes	No	10
7[a]	M	3.8	7.5	Anterior	JIA	Chronic	Surgical[c]	No	Yes	Long term	7.5
							Surgical[b]	No	Yes	Perioperative	10
8[a]	F	6.4	10.6	Anterior	JIA	Chronic	Surgical[c]	No	Yes	Long term	0
							Surgical[c]	No	Yes	Perioperative	0
9	F	7.0	12.3	Anterior	JIA	Chronic	Surgical[c]	No	Yes	Perioperative	10
10	M	5.9	9.3	Anterior	JIA	Chronic	Surgical[c]	No	Yes	Perioperative	7.5
11	F	3.5	10.4	Anterior	JIA	Chronic	Surgical[c]	No	Yes	Perioperative	7.5
12	F	14.4	14.4	Anterior	HLA-B27	Acute	Diagnostic	Yes	Yes	No	0
13	M	10.4	10.4	Anterior	HLA-B27	Acute	Diagnostic	Yes	Yes	No	0
14	M	5.9	6.0	Anterior	Herpes virus[d]	Acute	Diagnostic	Yes	No	No	0
15	M	14.6	14.8	Anterior	Fuchs'	Chronic	Surgical[b]	Yes	Yes	Perioperative	0
16	F	7.8	9.2	Anterior	Eci	Chronic	Surgical[c]	No	Yes	No	7.5
17[a]	F	10.1	12.2	Intermediate	Eci	Chronic	Surgical[c]	No	Yes	Perioperative	0
							Surgical[b]	No	Yes	Perioperative	12.5
18[a]	M	9.2	9.2	Intermediate	Eci	Chronic	Diagnostic	Yes	Yes	No	0
							Surgical[b]	No	Yes	Perioperative	0
19	F	10.5	10.7	Intermediate	Eci	Chronic	Diagnostic	Yes	Yes	No	0
20	M	6.1	6.1	Intermediate	Eci	Chronic	Diagnostic	Yes	No	No	0
21	M	5.3	5.4	Intermediate	Eci	Chronic	Diagnostic	Yes	Yes	No	0
22	M	5.4	5.4	Posterior	NMO	Acute	Diagnostic	Yes	No	No	0
23	M	6.7	6.8	Posterior	Eci	Chronic	Surgical[b]	Yes	No	Perioperative	0
24	F	11.2	14.0	Panuveitis	Eci	Chronic	Surgical[b]	No	No	Long term	20
25[a]	F	12.7	13.1	Panuveitis	Eci	Chronic	Diagnostic	No	Yes	Long term	0
							Surgical[c]	No	Yes	Long term	0

JIA=juvenile idiopathic arthritis; MTX=methotrexate; NMO=neuromyelitis optica/Devic's syndrome.
[a]For these patients 2 successive samples were available.
[b]Cataract surgery.
[c]Glaucoma surgery.
[d]Varicella-zoster virus.

Table 2. Cytokine, chemokine and adhesion molecule levels in aqueous humor of children with uveitis and in children with juvenile idiopathic arthritis-associated uveitis compared with controls

Mediator	Mediator concentrations in the aqueous humor compared with controls				Control group (n=6)
	Total uveitis group (n=25)		Juvenile idiopathic arthritis-associated uveitis group (n=11)		
	Mean[a]	P value	Mean[a]	P value	Mean[a]
	Range[b]		Range[b]		Range[b]
	No.[c]		No.[c]		No.[c]
IL-1β	<1		2		<1
	1-7	0.105	1-6	0.149	<1
	15		6		6
IL-2	33		46		<6
	6-705	0.041	6-589	0.037	6-35
	9		3		5
IL-4	15		24		2
	1-1407	0.158	1-1407	0.216	1-9
	8		4		2
IL-6	106		94		<3
	3->13 822	<0.001	13-5603	<0.001	3-9
	1		0		3
IL-10	6		3		<1
	1-114	0.020	1-68	0.149	1-2
	6		4		3
IL-12 p70	9		12		<5
	5-105	0.053	5-105	0.078	<5
	12		5		6
IL-13	10		11		<2
	2-128	0.027	2-92	0.048	2-7
	7		3		4

IL-18	13		15		<3
	3-72	0.009	3-68	0.010	3-8
	3		1		3
IFN-γ	7		9		<2
	2-104	0.035	2-104	0.037	<2
	11		4		6
TNF-α	5		9		1
	1-61	0.046	1-61	0.015	1-7
	6		1		4
sICAM	3710		3523		1028
	490->10 001	0.020	621->10 001	0.048	374-5669
	0		0		0
sVCAM	4506		4660		3286
	956->10 105	0.364	1286->10 105	0.350	947->10 105
	0		0		0
RANTES	96		93		13
	9-1175	0.001	9-282	0.002	9-61
	3		1		3
Eotaxin	6		6		6
	2-41	0.865	2-41	0.884	2-48
	8		4		1
IL-8	54		29		8
	5-1715	0.006	5-304	0.078	5-46
	3		2		2
IP-10	859		780		147
	52-3680	<0.001	198-2018	0.002	52-399
	0		0		0

IL=interleukin; IFN=interferon; TNF=tumor necrosis factor; sICAM=soluble intercellular adhesion molecule; sVCAM= soluble vascular cell adhesion molecule; RANTES=regulated on activation normal T-cell expressed and secreted; IP=interferon-inducible protein.
Sensitivity of the assay is 1.4 pg/ml for IL-1β, 1.8 for IL-2, 1.2 for IL-4, 2.4 for IL-6, 2.3 for IL-10, 4.3 for IL-12 p70, 1.0 for IL-13, 1.2 for IL-18, 9.1 for IFNγ, and 1.2 for TNFα. Sensitivity for sICAM (CD54) is 26.4 pg/ml, for sVCAM (CD106) 22.3, for RANTES (CCL5) 1.5, for Eotaxin (CCL11) 1.3, for IL-8 (CXCL8) 5.3, and for IP-10 (CXCL10) 1.0 (sensitivity data from de Jager *et al.*, 2005).
[a]Geometric mean concentration (pg/ml).
[b]Range of detectable measured samples (pg/ml).
[c]Number of samples in the undetectable range.

uveitis for all the 16 mediators studied. There were only 2 children with posterior uveitis and 2 children with panuveitis therefore no comparison was made between all 4 anatomic classifications. Furthermore, between samples from chronic (n=21) and acute (n=4) uveitis no significant differences were found for all 16 mediators, but levels of IP-10 and IL-2 tended to be higher in chronic uveitis (1013 pg/ml versus 361 pg/ml; p=0.068 and 47 pg/ml versus 5 pg/ml; p=.081 respectively).
Treatment with or without topical corticosteroids had no influence on the mediator levels in AqH of children with uveitis (n=20 versus n=5, respectively). Both groups were equally treated with systemic corticosteroids (perioperative or long term) and with MTX (p=.821 and p=.341, respectively). Cytokine levels of children treated with perioperative corticosteroids (n=9) did not differ significantly from those not treated with systemic corticosteroids (n=12). These two groups did not differ in treatment with topical corticosteroids and MTX (p=.603 and p=.396, respectively). Treatment with long-term systemic corticosteroids (n=4) or no systemic corticosteroids (n=12) at time of sample collection had no influence on the mediator levels in the AqH of children with uveitis. Both groups were equally treated with topical corticosteroids and with MTX (p=1.000 and p=.604, respectively). Children treated with MTX (n=11) at time of sample collection showed significantly lower levels of IL-8 (24 pg/ml versus 102 pg/ml, respectively, p=.021) and IL-10 (3 pg/ml versus 11 pg/ml, p=.008) than children not treated with MTX (n=14, Table 3). Both groups did not differ significantly in systemic (perioperative or long term) and topical treatment with corticosteroids (p=.567 and p=.341, respectively). Of all children treated with MTX, 9 (9/11, 82%) had JIA-associated uveitis and 2 (2/11, 18%) had chronic uveitis of unknown etiology; all samples were collected during surgery. The mean duration of MTX treatment before sample collection was 2.2 years (median: 1.6 years, range: 0.2–8.4 years) with a mean dose of 10 mg/week (median: 10.6 mg/week, range: 7.5–20 mg/week).
When comparing samples from children before any kind of systemic treatment (corticosteroids and/or MTX) was started (n=8) with samples from children who were already systemically treated (n=17), significantly higher levels of IL-8 were found in the first group (129 pg/ml versus 36 pg/ml, p=.019) and IL-10 tended to be higher in that group (13 pg/ml versus 4 pg/ml, p=.097).
Significantly lower levels of IL-10 were observed in patients with quiet stage uveitis samples (collected during surgery, n=16) compared with active uveitis samples (collected for diagnostic purposes, n=9; 3 pg/ml versus 15 pg/ml; p=.027). Also, IL-8 was found to be lower in quiet uveitis samples (31 pg/ml versus 144 pg/ml; p=.004). Significantly more children had JIA-associated uveitis in the quiet

uveitis group (11/16) than children in the active phase of the disease (0/9, p=.001). Children with active uveitis were significantly less treated with MTX (0/9) than children with quiet uveitis (11/16, p=.001). The definite diagnosis of patients with diagnostic AqH taps were herpes virus infection (n=1), HLA-B27 (n=2), Devic's neuromyelitis optica (n=1) and unknown etiology (n=5). All active samples, except one, were taken during the first 3 months after the diagnosis of uveitis.

Samples collected during surgery (quiet uveitis samples) had signifi-cantly higher levels of IL-2, IL-6, IL-13, IL-18, IFN-γ, TNF-α, sICAM-1, RANTES, IL-8 and IP-10 than AqH samples of controls.

Interleukin-10 was also found at a significantly lower level in AqH samples taken after more than 3 months after the diagnosis of uveitis (n=15) than in AqH samples taken during the first 3 months after the diagnosis of uveitis (n=10; 3 pg/ml versus 28 pg/ml, respectively, p=.016). The first group was significantly more often treated with MTX at time of sample taking (11/15 versus 0/10, p=.001). Of all children in whom the samples were taken during the first 3 months after the diagnosis of uveitis none had JIA-associated uveitis and 11 out of 15 children in the group in whom samples were taken after more than 3 months had JIA-associated uveitis (p=.001). All other 15 mediators tested were equal in both groups.

JIA was the most common systemic disease in our population (n=11). Significantly higher levels of IL-2, IL-6, IL-13, IL-18, IFN-γ, TNF-α, sICAM-1, RANTES and IP-10 were found in AqH of children with JIA-associated uveitis than in controls (Table 2). Interleukin-8 and IL-10 levels in AqH of these children did not differ significantly from controls, whereas these cytokines were significantly increased in the total uveitis group compared with controls. All AqH mediators from children with JIA-associated uveitis were similar to levels measured in children with other uveitis entities (n=14). Children with JIA-associated uveitis were significantly more often treated with MTX (9/11) than children with uveitis not associated with JIA (2/14, p=.001). When comparing AqH samples of children with JIA-associated uveitis (n=11) with only those with uveitis of unknown etiology (n=9), no significant differences were found as well.

No differences were found between cytokine levels in AqH samples of patients with different types of JIA: persistent oligoarticular JIA (n=6), extended oligoarticular JIA (n=2) or polyarticular JIA (n=3).

At the time of sample collection only one girl with JIA-associated uveitis was treated with anti-TNF (etanercept twice a week 12 mg subcutaneously) and MTX. Her TNF level in AqH was 14 pg/ml.

Repeated samples of the same eye were available for 6 patients (nos. 3, 7, 8, 17, 18 and 25; Table 1). The first samples were taken during surgery (n=4) or for a

Table 3. Cytokine, chemokine and adhesion molecule levels in aqueous humor of children with uveitis treated with methotrexate compared with children with uveitis not treated with methotrexate

Mediator	Mediator concentrations in the aqueous humor of children with uveitis		P value
	Treated with methotrexate (n=11)	Not treated with methotrexate (n=14)	
	Mean[a]	Mean[a]	
	Range[b]	Range[b]	
	No.[c]	No.[c]	
IL-1β	2	1	
	1-6	1-7	0.202
	5	10	
IL-2	60	21	
	6-614	6-705	0.244
	3	6	
IL-4	29	9	
	1-1407	1-1407	0.344
	4	4	
IL-6	74	140	
	11-5603	3->13 822	0.344
	0	1	
IL-10	3	11	
	1-17	1-114	0.008
	4	2	
IL-12 p70	17	6	
	5-105	5-98	0.107
	4	8	
IL-13	14	7	
	2-104	2-128	0.317
	3	4	

IL-18	14	12	
	3-68	3-72	0.536
	2	1	
IFN-γ	11	4	
	2-104	2-89	0.183
	4	7	
TNF-α	9	3	
	1-61	1-37	0.107
	2	4	
sICAM	3298	4069	
	621->10 001	490->10 001	0.344
	0	0	
sVCAM	4537	4482	
	1286->10 105	956->10 105	0.809
	0	0	
RANTES	64	132	
	9-261	9-1175	0.134
	2	1	
Eotaxin	6	6	
	2-18	2-41	0.809
	4	4	
IL-8	24	102	
	5-99	5-1715	0.021
	2	1	
IP-10	863	856	
	204-2018	52-3680	0.767
	0	0	

IL=interleukin; IFN=interferon; TNF=tumor necrosis factor; sICAM=soluble intercellular adhesion molecule; sVCAM= soluble vascular cell adhesion molecule; RANTES=regulated on activation normal T-cell expressed and secreted; IP=interferon-inducible protein.
Sensitivity of the assay is 1.4 pg/ml for IL-1β, 1.8 for IL-2, 1.2 for IL-4, 2.4 for IL-6, 2.3 for IL-10, 4.3 for IL-12 p70, 1.0 for IL-13, 1.2 for IL-18, 9.1 for IFNγ, and 1.2 for TNFα. Sensitivity for sICAM (CD54) is 26.4 pg/ml, for sVCAM (CD106) 22.3, for RANTES (CCL5) 1.5, for Eotaxin (CCL11) 1.3, for IL-8 (CXCL8) 5.3, and for IP-10 (CXCL10) 1.0 (sensitivity data from de Jager *et al.*, 2005).
[a]Geometric mean concentration (pg/ml).
[b]Range of detectable measured samples (pg/ml).
[c]Number of samples in the undetectable range.

diagnostic procedure (n=2). All second samples were taken during surgery (n=6). The median time interval between the first and second sample was 1.5 years (range: 0.2–2.3 years). Significantly higher levels of IL-6 were observed in the first samples compared with the second samples (122 pg/ml versus 12 pg/ml; p=.046). This significant difference was not found when we excluded the diagnostic samples.

Discussion

This is the first study that shows that multiple intraocular cytokines, chemokines and soluble adhesion molecules are elevated in AqH of children with uveitis. The elevated levels were observed for cytokines associated with T helper 1 (Th1; IL-2, IFN-γ, TNF-α), Th2 (IL-13) and T regulatory (Tr; IL-10) response. The reason that we did not find a predominance of Th1 cytokine profile, as previously described in the literature, might be explained by the mixed study population.[2;4] However, borderline higher levels of IP-10 and IL-2 were found for the chronic course (p=.068 and p=.069, respectively). This observation might suggest a predominant Th1 response in children with chronic uveitis. Furthermore, in AqH of children in whom the samples were collected before start of systemic treatment, we saw higher levels of IL-8, a pro-inflammatory cytokine, compared with AqH of children in whom treatment with systemic corticosteroids and/or MTX was already started.

Interleukin-8 (CXCL8) is a chemokine with profound effects on neutrophils, is chemotactic for T lymphocytes and can induce surface expression of adhesion molecules and is known as a pro-inflammatory cytokine.[12-14] Interleukin-10 is an anti-inflammatory cytokine which prevents for the development of autoimmune diseases.[15;16] The observation that higher levels of IL-10 and IL-8 were detected in samples collected for diagnostic purpose (active uveitis) compared with samples collected during ocular surgery (quiet uveitis) might implicate that these cytokines are mainly involved in active uveitis. Interleukin-10 was higher in samples taken during the first 3 months after the diagnosis of uveitis. These samples were mainly (8 out of 10) collected for diagnostic purposes before the start of systemic treatment. Therefore IL-10 might be involved in the early stage of the disease process, in active uveitis, or both. The lower levels of IL-8 in uveitis samples collected during ocular surgery compared with diagnostic samples might be explained by the fact that the ocular inflammation was at that point quiet (due to treatment). However, IL-8 and IL-10 were found in a lower range in children treated with MTX. From our data it is not clear whether the early stages or active uveitis are responsible for higher levels of IL-8 and IL-10 or,

alternatively, whether the absence of treatment with MTX causes this difference. Despite the absence of clinical signs of active inflammation, elevated cytokine levels were found in the samples obtained during surgical procedures compared with controls. This might implicate that when the uveitis is in clinical remission (no inflammatory cells in the anterior chamber or other inflammatory features), there is an ongoing immune response in the eye based on the elevated cytokines. When comparing mediator levels in AqH collected during successive surgical interventions in the same eye, no change in (inflammatory) cytokines was found. As such, this is reassuring because it indicates that the surgical intervention itself does not lead to a trauma induced cytokine response.

In the present study we did not find differences in cytokine pattern between the different types of JIA. Patients with systemic JIA have higher serum levels of IL-6 than other forms of JIA.[17] Our series does not include samples of uveitis patients with systemic JIA, because uveitis is a very rare feature of systemic JIA. Furthermore, the JIA samples used in this study were collected during cataract or glaucoma surgery. So all these patients had surgery requiring complications of JIA-associated uveitis and therefore they might not be representative of the total JIA-associated uveitis population.

Limitations of this study include the restricted number of samples which precludes meaningful comparison of specific disorders or subcategories of disorders such as anatomic classification, course of uveitis and systemic diseases. Furthermore, our control group was not perfectly age-matched and low in number. The reason for this is that AqH samples of children with or without uveitis are not readily available. At the time of sample collection the children in the control group were younger than the children with uveitis. However, when we compared our control samples with the adult controls of the study of our colleagues, no major differences were found, except for IL-6, sICAM-1 and sVCAM-1.[18] More detailed studies on the age dependency of cytokine profiles in AqH of uveitis patients are currently underway.

For future studies, it will be important to collect and examine larger series of AqH samples of children with uveitis, in order to make comparisons between different systemic diseases (for example JIA-associated versus HLA-B27 positive uveitis) among the 4 anatomical classifications of uveitis and other comparisons possible. We did not find significant differences between cytokine levels in AqH of JIA-associated uveitis and other uveitis entities. Based on this relatively small study population we cannot conclude whether there is a common pathway in juvenile uveitis, irrespective of the underlying cause. It would be interesting to examine this in a bigger study population with a special regard for IL-8 and IL-10. Furthermore,

it would be interesting to compare cytokine and total IgG levels in AqH with those in serum of children with uveitis, to make a discrepancy between local production and influx from elsewhere due to blood aqueous barrier breakdown.
In the last decades the knowledge of the immune system has improved and treatment of inflammatory diseases with biological agents has become available. Biologics are drugs directed against specific cytokines or their receptors.[19] In children, treatment of JIA with anti-TNF has been successful for arthritis. In the near future, treatment with several other biologics might become available. Therefore more insight into the cytokine profile in childhood uveitis is warranted.
In conclusion, our data suggest that a spectrum of cytokines, chemokines and soluble adhesion molecules in the AqH of children with uveitis are involved in the pathogenesis of uveitis. These mediators are present irrespective of active or inactive uveitis and without clear predominance of a Th1 or Th2 associated cytokine profile. Whether the IL-10 and IL-8 levels in AqH appear to be related to uveitis activity, early or late phase of the course of uveitis or systemic treatment with MTX needs further investigation. Further studies will be required to elucidate the exact role of these mediators in the pathogenesis of different uveitis entities, especially JIA, and specific treatment strategies.

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Chapter 7

Distinct cytokine patterns in the aqueous humor of children, adolescents and adults with uveitis

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(Accepted for publication in Ocul Immunol Inflamm)

Abstract

Purpose: To determine the immune mediator profile in relation to age in the aqueous humor (AqH) of patients with uveitis.
Methods: AqH of children, adolescents and adults with uveitis was analyzed for 16 immune mediators.
Results: No significant differences were found for IL-8, RANTES and IP-10. The concentrations of the remaining 13 mediators were significant lower in adults compared with children and adolescents, except for IL-6 which was higher.
Conclusions: Various immune mediators are present in higher concentrations in AqH of children and adolescents with different uveitis entities compared with that of adults, except IL-6, which was higher in adults.

Introduction

Uveitis in childhood differs in many aspects from that in adults. In our experience, and that of other ophthalmologists, a more severe clinical course of uveitis and also a different spectrum of complications are observed in children than in adults with uveitis.[1-3] Also, the inflammatory response after ocular surgery in adults with uveitis is generally well controlled, whereas in children it might be challenging.[4;5] Several studies, including ours, have shown that cytokine levels are elevated in the aqueous humor (AqH) of patients with uveitis.[6-8] The purpose of this study was to investigate whether there is a difference in immune response in the eye between children, adolescents and adults. Therefore, we compared the profile of cytokines, chemotactic cytokines (chemokines) and soluble adhesion molecules in the AqH of patients with uveitis in relation to age.

Materials and methods

Patients. This research followed the tenets of the Declaration of Helsinki and was approved by our institutional review board. Written informed consent was obtained from each patient and/or parent after explanation of the nature of the study.

AqH samples were collected as described previously, stored immediately at -80°C in sterile screw-cap tubes and thawed directly before analysis within 4 years of collection.[9] This technique ensures the preservation of all mediators in the sample for analysis without degradation. AqH samples of 63 patients with uveitis were used. These samples were obtained during surgery (cataract n=16, glaucoma n=10, vitrectomy n=2, scleral buckling n=1) or were collected for diagnostic purposes (n=34). All surgical samples were collected when the uveitis was under control and the diagnostic samples were taken when the intraocular inflammation was active.

The following clinical data were recorded for each patient: age at diagnosis of uveitis, age and treatment at the time of sample collection, localization of uveitis, type of sample (surgical or diagnostic) and underlying systemic disease.

All patients were divided into three age groups according to the World Health Organization (WHO) classification: children (2 to 9 years of age), adolescents (10 to 19 years of age) and adults (20 years of age or older). No samples were available from infants (0-2 years of age).

Immunoassay. We analyzed the AqH samples in a multiplex immunoassay as described previously.[10] In each 50 μl sample, we analyzed 16 mediators; interleukin-1 (IL-1), IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p-70, IL-13, IL-18, interferon-γ

(IFN-γ), tumor necrosis factor-α (TNF- α), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), RANTES (Regulated on Activation, Normal T-cell Expressed, and Secreted; CCL5), Eotaxin (CCL11) and interferon-inducible 10kDa protein (IP-10; CXCL10). Concentrations above or below the detection limit were given as the highest or lowest detectable value. For statistical analysis concentrations below the detection limit were converted to a value of 0.5 x the lowest point of the calibration curve.

Statistical analysis. Statistical analysis of the data was performed by using the SPSS statistical software package version 12.0.1 (SPSS Inc., Chicago, IL). The Kruskal-Wallis and the Mann-Whitney U tests were used to compare the nonparametric means and the ANOVA test was used to compare the parametric means of the different groups. The Pearson Chi-square test or the Fischer's exact test was used to compare possible associations between categorical variables where appropriate. P values below .05 were considered to be statistically significant.

Statement of ethics. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results

Aqueous humor was collected from 63 patients with uveitis (children: n=12; adolescents: n=16 and adults: n=35, Table 1). The median age at sample collection was 6.1 years for children (range 5.2 to 9.3 years), 12.5 years for adolescents (range 10.4 to 17.3 years) and 43.7 years for adults (range 20.4 to 81.1 years). The 3 different age groups did not significant differ in the number of samples collected for diagnostic purpose (active uveitis) or during ocular surgery (quiet uveitis), and neither in systemic treatment with prednisone. However, there were differences between these 3 groups concerning the age at diagnosis of uveitis, gender, localization and underlying cause of uveitis and the treatment with topical corticosteroids and methotrexate (MTX, Table 1).

The concentrations of all 16 mediators in AqH according to age are shown in Table 2. Between the 3 age groups significant differences were found for the concentration of 13 out of all 16 mediators, but not for IL-8, RANTES and IP-10. Twelve of these 13 mediators were found in lower concentrations in adults compared with children (not significant for IL-10) and adolescents, but IL-6 concentration was higher in adults than in children and adolescents (p=.008 and p=.056 respectively). Between children and adolescents, no differences were found for all 16 mediators. High concentrations of IL-6 (i.e. above the detection limit of 13,000 pg/ml) were

Table 1. Clinical data of all patients

		Children 2 – 9 yrs (n=12)	Adolescents 10 – 19 yrs (n=16)	Adults ≥20 yrs (n=35)	P value
Age at sample collection (yrs)	Mean	6.8	13.1	46.9	
	Median	6.1	12.5	43.7	NA
	Range	5.2-9.3	10.4-17.3	20.4-81.1	
Age at diagnosis of uveitis (yrs)	Mean	5.5	9.7	43.6	
	Median	5.6	10.2	41.3	<0.001
	Range	1.9-9.2	3.4-16.7	10.6-80.3	
Gender (%)	Female	3 (25)	12 (75)	18 (51)	0.027
	Male	9 (75)	4 (25)	17 (49)	
Sample (%)	Surgical	7 (58)	10 (63)	12 (34)	0.107
	Diagnostic	5 (42)	6 (38)	23 (66)	
Localization of uveitis (%)	Anterior	7 (58)	10 (63)	8 (23)	
	Intermediate	3 (25)	1 (6)	5 (14)	0.020
	Posterior	1 (8)	1 (6)	13 (37)	
	Panuveitis	1 (8)	4 (25)	9 (26)	
Underlying cause of uveitis					
Infectious	Toxoplasmosis	0	1	6	
	Herpes, ARN	0	0	2[a]	
	Herpes, keratoconjunctivitis	1[a]	0	1[b]	0.226
	Herpes, anterior uveitis	0	0	2[c]	
	Borrelia	0	0	1	
	Fuchs'	0	1[d]	0	
Systemic	JIA	5	7	0	
	Sarcoidosis	0	0	3	0.001
	Behçet's disease	0	0	1	
Others	HLA-B27	0	2	1	
	Birdshot	0	0	1	
	Neuroretinitis	0	0	1	0.462
	Devic's neuromyelitis optica	1	0	0	
	Unknown origin	5	5	16	
Treatment					
Topical (%)	Corticosteroids	8 (67)	14 (88)	10 (29)	<0.001
Systemic (%)	Prednisone	1 (8)	3 (19)	3 (9)	0.557
	MTX	5 (42)	6 (38)	1 (3)	<0.001

JIA=juvenile idiopathic arthritis; MTX=methotrexate; NA=not applicable.
[a]Varicella-zoster virus.
[b]Herpes simplex virus.
[c]Cytomegalovirus, not immune-compromised.
[d]Positive for aqueous humor Rubella virus-specific antibody production.

Table 2. Cytokine, chemokine and adhesion molecule level in aqueous humor of children, adolescents and adults with uveitis

	Mediator concentration (pg/ml) in aqueous humor samples of patients with uveitis						
	Children 2-9 yrs (n=12)	**Adolescents 10-19 yrs (n=16)**	**Adults ≥20 yrs (n=35)**	**P value**			
Mediator	Geom. mean[a] Median Range[b] No.[c]	Geom. mean[a] Median Range[b] No.[c]	Geom. mean[a] Median Range[b] No.[c]	All three groups	Children versus Adolescents	Children versus Adults	Adolescents versus Adults
IL-1	1.2 0.7 0.7-4.9 7	1.3 0.7 0.7-6.6 10	0.8 0.7 0.7-6.7 33	0.010	0.873	0.005	0.006
IL-2	21.6 7.9 2.8-614.2 5	32.4 36.1 2.8-705.5 6	3.8 2.8 2.8-44.3 29	0.001	0.599	0.007	<0.001
IL-4	8.8 4.1 0.6-389.0 5	17.5 26.1 0.6-1 407.4 4	0.8 0.6 0.6-41.3 32	<0.001	0.478	<0.001	<0.001
IL-6	58.8 85.2 1.5-310.8 1	127.2 113.8 1.5->13 821.8 1	542.3 239.5 39.5->13 821.8 0	0.015	0.599	0.008	0.056
IL-8	28.2 39.2 2.4-1 136.2 3	88.6 73.0 10.4-1 715.2 0	26.3 20.2 2.4->4 543.7 13	0.074			
IL-10	4.7 8.7 0.4-113.6 4	7.6 11.6 0.4-68.4 2	2.2 0.4 0.4->4 974.5 26	0.048	0.478	0.163	0.016
IL-12	8.2 7.1 2.3-62.2 6	9.3 4.3 2.3-105.0 8	2.4 2.3 2.3-20.2 34	<0.001	0.873	<0.001	<0.001
IL-13	7.1 8.4 0.8-104.4 4	8.0 12.5 0.8-128.0 6	1.1 0.8 0.8-18.7 30	<0.001	0.982	<0.001	<0.001

IL-18	9.6 10.5 1.4-42.8 2	12.3 19.6 1.4-71.8 4	3.5 1.4 1.4-78.7 23	0.003	0.599	0.011	0.003
IFN-γ	5.5 7.2 1.0-54.8 6	7.8 10.4 1.0-104.4 6	1.5 1.0 1.0-51.8 29	0.001	0.664	0.011	<0.001
TNF-α	3.8 5.0 0.5-28.3 4	4.7 6.5 0.5-60.6 3	0.7 0.5 0.5-14.7 29	<0.001	0.664	<0.001	<0.001
sICAM	3076.4 4 549.7 489.9->10 000.8 0	4090.0 4 781.2 690.8->10 000.8 0	418.4 349.4 33.8-7 980.9 0	<0.001	0.631	<0.001	<0.001
sVCAM	4139.7 5 724.6 956.2->10 105.3 0	4571.5 6 498.0 1035.7->10 105.3 0	825.4 746.3 156.0->10 105.3 0	<0.001	0.537	<0.001	<0.001
RANTES	106.0 108.0 4.7-1 175.1 1	65.6 113.3 4.7-761.8 3	53.7 85.5 4.7-1 016.3 11	0.746			
Eotaxin	5.0 6.9 1.1-34.7 4	5.4 8.6 1.1-40.7 6	1.4 1.1 1.1-28.2 32	<0.001	0.909	<0.001	<0.001
IP-10	647.9 830.1 52.3-3 680.4 0	1 308.8 1 362.1 203.6->8 926.8 0	906.0 1 053.8 39.9->6 826.8 0	0.405			

IL=interleukin; IFN=interferon; TNF=tumor necrosis factor; sICAM=soluble intercellular adhesion molecule; sVCAM= soluble vascular cell adhesion molecule; RANTES=regulated on activation of normal T-cell expressed and secreted; IP=interferon-inducible protein.
Sensitivity of the assay is 1.5 pg/ml for IL-1β, 1.8 for IL-2, 1.2 for IL-4, 2.4 for IL-6, 2.3 for IL-10, 4.3 for IL-12 p70, 1.0 for IL-13, 1.2 for IL-18, 9.1 for IFNγ, and 1.2 for TNFα. Sensitivity for sICAM (CD54) is 26.4 pg/ml, for sVCAM (CD106) 22.3, for RANTES (CCL5) 1.5, for Eotaxin (CCL11) 1.3, for IL-8 (CXCL8) 5.3, and for IP-10 (CXCL10) 1.0 (sensitivity data from de Jager *et al*., 2005).
[a]Geometric mean.
[b]Range of detectable measured samples.
[c]Number of samples in the undetectable range.

found in 8 samples, 2 adolescents with HLA-B27-associated uveitis and 6 adults: 1 with HLA-B27-associated uveitis, 1 with Varicella-zoster virus-induced acute retinal necrosis, 1 with Behçet's disease and 3 patients with uveitis of unknown origin. All these 8 samples were taken for a diagnostic purpose (active uveitis).

Discussion

This study shows that aqueous humor samples of adults with uveitis have significant lower concentrations of several immune mediators compared with samples from children and adolescents. These immune mediators play a role in both the T helper 1 (Th1; IL-2, IL-12, IL-18, IFN-γ, TNF-α), the Th2 (IL-4, IL-13) and the T regulatory (Tr; IL-10) response. The 3 immune mediators that did not differ significantly between the 3 age groups were all chemokines (IL-8, RANTES and IP-10).

Interleukin-6, a pro-inflammatory cytokine was the only immune mediator in this study which showed higher concentrations in AqH of adults. The highest concentrations of IL-6 were found in patients with active, acute HLA-B27-associated uveitis, in a patient with Behçet's disease and in patients with severe infectious uveitis such as acute retinal necrosis (ARN). However, other pro-inflammatory cytokines such as IL-1, IL-2, IL-4, IL-18 and IFN-γ were significantly lower in adults than in children and adolescents and IL-8 was found in equal concentrations.

From our data it is not possible to conclude whether the difference in immune mediator concentration between the 3 groups is a result of a difference in immune response according to the age of the patients or whether it is related to the differences in underlying cause of uveitis. In a general uveitis population the associated systemic diseases are different between children and adults with uveitis. In this study, JIA was the most common cause of uveitis in children and adolescents and only about 10% of all cases had an infectious etiology, whereas in the adult group sarcoidosis was the most common systemic disease and more than one third of the samples were from infectious origin. However, the disease activity between the 3 groups was comparable since similar percentages of diagnostic samples (active uveitis) were found in the adult group compared with the younger 2 groups.

In this study we found lower concentrations of IL-10 in the AqH of the adult group compared with adolescents and equal concentrations of IL-8 compared with children and adolescents. In a previous study we found lower concentrations of IL-8 and IL-10 in the AqH of children treated with MTX.[8] However, in the current

study, the lower concentrations of IL-10 in adults cannot be explained by the influence of treatment with MTX since significantly fewer patients in the adult group were treated with this drug compared with the adolescent group. Furthermore, the adult group was significantly less treated with topical corticosteroids which can be explained by the fact that more posterior uveitis was present in the adult group.

The limitations of this study include the restricted number of samples and the diversity of our study population which precludes a meaningful comparison of specific disorders or subcategories of disorders. For the above reasons, no effort have been made to adjust for the different ages at the time of the diagnosis of uveitis, the localization and underlying course of uveitis and the treatment with topical corticosteroids and MTX. For future studies it would be interesting to investigate the effect of age in a larger cohort in order to substantiate the effect of age which we found in this small study.

In conclusion, we observed different immune mediator responses in the AqH of uveitis patients in different age groups. The majority of pro-inflammatory immune mediators were present in a higher concentration in the AqH of children and adolescents compared with that of adults, with the exception of IL-6. Whether these differences are a reflection of age or of age related underlying causes of uveitis needs further investigation in a large cohort.

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Chapter 8

Keratitis and arthritis in children with sarcoidosis

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(Accepted for publication in Br J Ophthalmol)

Abstract

A preschool girl presented with keratitis and multiple subepithelial round corneal nebulae in combination with uveitis. Additionally, she was suffering from arthritis, fever and skin rash. After treatment, the keratitis disappeared but the corneal nebulae persisted. Although she was initially diagnosed with juvenile idiopathic arthritis, sarcoidosis was also suspected. Later on, she developed posterior segment involvement including multifocal choroiditis and choroidal granuloma. After several years the diagnosis of sarcoidosis was confirmed by renal and skin biopsies.

In addition, we noted focal keratitis with subsequent nebulae in 2 other children with preschool sarcoidosis.

We conclude that keratitis with multiple subepithelial corneal nebulae might occur in the early stage of sarcoidosis in preschool children.

Case report

A three-year-old girl was referred by her pediatric rheumatologist for screening for uveitis due to a diagnosis of suspected juvenile idiopathic arthritis. She suffered from attacks of fever, polyarthritis and a maculopapular skin rash which also suggested a diagnosis of sarcoidosis. However, at that time the synovial biopsy showed a negative result for granulomatous inflammation. There were no ophthalmologic complaints. She had full visual acuity in both eyes. On slit lamp examination, multiple subepithelial corneal nebulae and focal active keratitis were observed as well as bilateral anterior uveitis. At the lumbus, there were small yellow conjunctival nodules suspected of being granulomas. Funduscopy revealed no abnormalities of the posterior segment. She underwent various laboratory examinations including full blood counts, antinuclear antibodies (ANA) and angiotensin-converting enzyme (ACE), assessment for tuberculosis and radiological chest examinations the results of which were all within normal limits. The keratitis and anterior uveitis responded to treatment with topical corticosteroids. In the mean time she was treated for her arthritis with methotrexate and later on with etanercept.
After four years she developed renal failure. Renal and skin biopsy confirmed the diagnosis of sarcoidosis. At that time, slit lamp examination showed subepithelial corneal nebulae. At funduscopy, multiple yellow choroidal lesions were also observed.
The parents gave permission for publication of the clinical pictures.

Questions

1. Describe the corneal lesions
2. What are the yellow lesions of the retina?
3. Which ocular features differentiate between the diagnosis of sarcoidosis and JIA?

Answers

1. The corneal lesions present as asymptomatic inconspicuous subepithelial round lesions with focal active keratitis. After treatment with topical corticosteroids, the keratitis disappears but the subepithelial round nebulae persist.
   Previously, keratitis was sporadically reported in pediatric sarcoidosis but the persistent nebulae have so far not been described.
2. The yellow chorioretinal lesions are probably small choroidal granulomas. The appearance and histology of these lesions are similar to those of Dalen-Fuchs

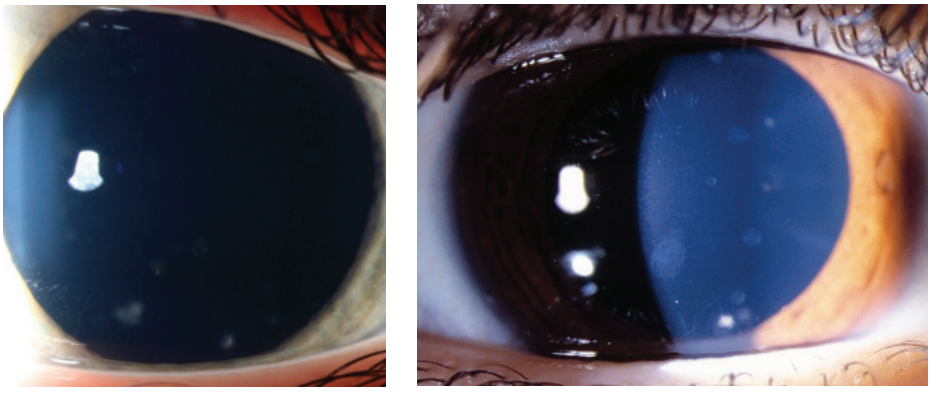

Figure 1 A. Keratitis and small subepithelial round nebulae scattered over the cornea in a girl with biopsy-proven sarcoidosis. **B**. Persistent corneal nebulae after keratitis in a boy with biopsy-proven sarcoidosis.

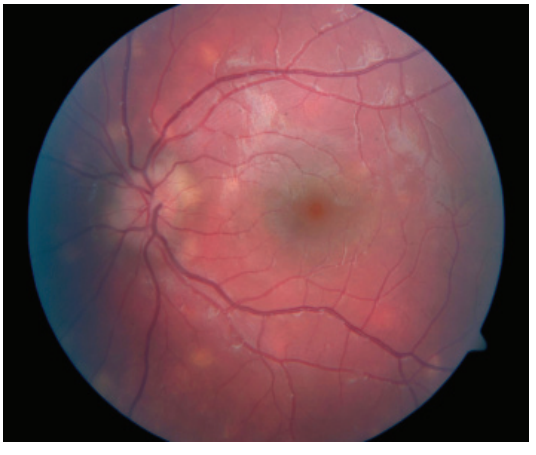

Figure 2. Choroidal granulomas in a girl with biopsy-proven sarcoidosis.

nodules of sympathetic ophthalmia. Large granulomas of the choroid might resemble choroidal tumors.

In our patient, choroidal lesions developed 4 years after the onset of ocular disease.

3. The clinical characteristics of juvenile idiopathic arthritis include anterior uveitis without posterior segment involvement. In sarcoidosis, all parts of the eye may be involved in the inflammation. Posterior segment involvement in sarcoidosis is typical and is characterized by multifocal choroiditis, choroidal granulomas, vasculitis and perivascular sheathing.

Discussion

We report on focal keratitis complicated by subepithelial corneal nebulae and uveitis in a girl with biopsy-proven sarcoidosis. She suffered from fever, arthritis and skin rash, which are frequent systemic symptoms of preschool sarcoidosis.[1-5] Our patient developed posterior segment involvement 4 years after the onset of ocular disease, specifically the formation of multiple small choroidal granulomas, features typically associated with sarcoidosis.[6;7] Although the diagnosis of sarcoidosis was suspected, it took at least 4 years before this suspicion could be confirmed by biopsy. In addition, we noted focal keratitis with subsequent nebulae in an additional 2 children with preschool sarcoidosis.

Sarcoidosis is difficult to diagnose in preschool children.[1-5;8] These children frequently present with rash, arthritis and uveitis, similarly to our patients. The corneal opacities occurred in all our patients with preschool childhood sarcoidosis, but were not present in the older children with biopsy-proven sarcoidosis seen in our institution (n=2). However, whether these corneal changes are really symptom-typical of preschool sarcoidosis cannot be concluded from only three patients. Various ocular manifestations of sarcoidosis in childhood have been described in the past, but keratitis with multiple nummular subepithelial infiltrates was not mentioned in a review of 26 children with sarcoidosis.[9] These corneal opacities are inconspicuous and might therefore easily have been overlooked. So far, only very sporadic cases with interstitial keratitis and keratoconjunctivitis as presenting symptoms of pediatric sarcoidosis have been reported.[10]

We conclude that keratitis with multiple subepithelial corneal nebulae might occur in the early stage of sarcoidosis in children. We recommend considering the diagnosis of sarcoidosis in children with arthritis and this specific corneal involvement.

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Chapter 9

Rubella virus–associated uveitis in a nonvaccinated child

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Abstract

Purpose: To report presumed Fuchs heterochromic uveitis (FHU) associated with Rubella virus (RV)-specific intraocular antibody production in a child who was not vaccinated against rubella.
Design: Observational case report.
Methods: We examined a 13-year-old boy with chronic anterior uveitis complicated by mature cataract. Two aqueous humor (AH) samples taken with an interval of four weeks were analyzed for intraocular antibody production against RV by calculation of the Goldmann-Witmer coefficient.
Results: The patient showed all the clinical signs for FHU: iris atrophy, stellate keratic precipitates, and cataract. Analysis of the AH demonstrated intraocular antibody production against RV in two sequential samples.
Conclusions: The data show that RV-associated uveitis can already present during childhood. Moreover, this finding suggests that nonvaccinated children may be at risk to develop uveitis after RV infection.

We describe a case of presumed Fuchs heterochromic uveitis (FHU) with rubella virus (RV)-specific antibody production in the aqueous humor (AH) in a nonvaccinated child.

A 13-year-old boy was referred because of unilateral uveitis complicated by mature cataract. Ophthalmologic examination revealed a visual acuity in the left eye of hand movements. Slit-lamp examination disclosed stellate keratic precipitates diffusely scattered across the corneal endothelium and mature cataract. Few cells were seen in the anterior chamber and one small posterior synechia was observed. No hyperemia of the conjunctiva was found. The patient was referred to a pediatrician, but there were no indications for systemic disease. Despite the small posterior synechia, the clinical characteristics suggested FHU. An AH sample taken for diagnostic purposes was negative for intraocular antibody production against Herpes simplex virus, Varicella zoster virus, and *Toxoplasma gondii*, but positive for RV, as determined by Goldmann-Witmer coefficient (GWC 31.93). The parents indicated that the patient had been refrained from vaccination for religious reasons, but they did not recall their child having had rubella. One month later, the patient's cataract was treated by phacoemulsification and intraocular lens implantation. The optimal postoperative visual acuity of the left eye was 6/5 (Snellen). A second AH sample collected during surgery was also positive for RV-specific antibody production (GWC 114.23).

The absence of posterior synechiae before surgery is considered to be one of the criteria of FHU.[1] However, because the incidence of pediatric FHU is low (reportedly less than 1%), little is known about the clinical presentation of FHU in this age group.[2] Possibly, posterior synechiae are formed in RV-induced FHU in the pediatric population.

RV infection may occur without clinical signs; the incidence of subclinical infections has been estimated as high as 25%.[3] The most important complication is a prime infection during pregnancy, which may give rise to congenital rubella syndrome (CRS) in the unborn child. In addition to severe systemic consequences such as cardiovascular defects and deafness, CRS may also include serious ocular abnormalities such as congenital cataract and pigmentary retinopathy.[3;4]

With the introduction of vaccination against RV in the Netherlands (since 1974 for school children and 1987 for all 14-month-old children), the incidence of rubella and CRS has declined significantly.[4] However, because of the presence of antivaccination groups based on religious incentives, rubella epidemics still occur in the Netherlands.[4]

The relationship between FHU and RV is not yet clear. Intraocular antibody production against RV is seen in almost 100% of FHU cases.[5] This might suggest that the intraocular immune response against RV is involved in the pathogenesis of this type of uveitis. One may speculate that because of vaccination, the incidence of (presumed) FHU will decrease.

Our finding of ocular inflammation in combination with intraocular RV antibody production might indicate that a RV infection may present as isolated uveitis, possibly FHU, later in life, and that awareness of this ocular disease in unvaccinated populations should remain.

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Chapter 10

Summary, conclusions and considerations

Summary

The aim of this study was to gain more insight into the development of complications in childhood uveitis and to evaluate the treatment options for these mostly sight-threatening conditions with emphasis on juvenile idiopathic arthritis (JIA)-associated uveitis **(chapter 2-5)**. The second aim was to investigate which cytokines are involved in the pathogenesis of pediatric uveitis by analyzing the presence of immune mediators in the aqueous humor of children with uveitis **(chapter 6-7)**.
In the course of the study, we also described 2 exceptional cases of pediatric uveitis. The first underlines the possibility of sarcoidosis as a differential diagnosis of JIA and the second addresses uveitis in a nonvaccinated child **(chapter 8-9)**.

Chapter 1 is a brief introduction to uveitis in childhood with emphasis on JIA-associated uveitis, its complications, treatment options, and screening recommendations.

In **chapter 2** we investigate which children with uveitis are at greatest risk of developing ocular hypertension and secondary glaucoma. This information is considered crucial, since secondary glaucoma is one of the most frequent causes of visual loss in childhood uveitis. Five years after the onset of uveitis, we found elevated intraocular pressure in 35% (22/62) and secondary glaucoma in 21% (13/62) of all children with uveitis. In children with JIA-associated uveitis the percentage of secondary glaucoma was almost twice as high (38%, 9/24). The anatomic localization of uveitis was shown to have influence on the time interval between the onset of uveitis and the development of elevated intraocular pressure. Children with posterior or intermediate uveitis had a shorter time interval (0.3 and 0.9 years respectively) than children with anterior or panuveitis (2.3 and 2.9 years respectively). However, none of the patients with elevated intraocular pressure with intermediate uveitis progressed to secondary glaucoma, whereas one third of the patients with anterior uveitis developed secondary glaucoma. Two thirds of all children with ocular hypertension or secondary glaucoma experienced elevated intraocular pressure in the first 2 years after the onset of uveitis.

We conclude that the most important risk factor for the development of secondary glaucoma in pediatric uveitis is having uveitis associated with JIA (including ANA-positive patients without evidence of arthritis). We recommend that the intraocular pressure should always be measured during frequent controls in all children with uveitis.

In **chapter 3** we compare two surgical treatment options for secondary glaucoma in JIA-associated uveitis: Ahmed glaucoma valve (13 eyes) and trabeculectomy (27 eyes) to find out which one is most successful. No permanent failures were found in the Ahmed glaucoma valve group and the mean survival time (duration of success of the glaucoma surgery) was 4.7 years in the trabeculectomy group. Cataract surgery was an important risk factor for failure since we found within the trabeculectomy group a mean survival time of 7.51 years for phakic eyes (n=9), 1.96 years for eyes with cataract extraction before trabeculectomy (n=6) and 2.81 years for eyes with cataract extraction after trabeculectomy (n=12). When we compared phakic eyes of the trabeculectomy group with all eyes of the Ahmed glaucoma valve group no difference in survival was found. However, when we compared all eyes of the trabeculectomy group operated on for cataract with the Ahmed glaucoma valve group, a significant difference in survival was found in favor of the Ahmed glaucoma valve group.

We conclude that the implant of a primary Ahmed glaucoma valve in aphakic or pseudophakic eyes of children with JIA-associated uveitis represents a better treatment option than trabeculectomy. However, in phakic eyes of children with JIA-associated uveitis, primary trabeculectomy can postpone the need for the implant of an Ahmed glaucoma valve by approximately seven and half years.

Chapter 4 is a study of the risk factors for the development of cataract requiring surgery in 53 children with JIA-associated uveitis. In this study we found that children with posterior synechiae at the time of diagnosis of uveitis had a significantly shorter time interval between the diagnosis of uveitis and the first cataract extraction than children without posterior synechiae (3.0 years versus 8.5 years, respectively). Treatment with methotrexate during the first year after the diagnosis of uveitis resulted in a significantly longer time interval between the diagnosis of uveitis and the first cataract extraction than without treatment with methotrexate (7.0 years versus 3.5 years, respectively). Treatment with periocular corticosteroid injections during the first year after the diagnosis of uveitis showed a trend, although not a significant one, towards a more rapid development of cataract requiring surgery. Whether systemic treatment with corticosteroids influences the time interval between the diagnosis of uveitis and the first cataract extraction could not be concluded from our results.

We conclude that the development of cataract requiring surgery in JIA-associated uveitis is caused by various factors. The presence of adherent posterior synechiae at the time of diagnosis of uveitis is strongly associated with the early development of cataract requiring surgery in children with JIA-associated uveitis.

This is in contrast to early treatment with methotrexate, which is associated with a delay in the development of cataract requiring surgery.

In **chapter 5** we evaluate whether the implantation of an intraocular lens increases the risk of developing long-term ocular complications in children with JIA-associated uveitis. We found no significant difference in complications including new onset of ocular hypertension and secondary glaucoma, cystoid macular edema, optic disc swelling and hypotony between aphakic and pseudophakic JIA eyes during the first 10 years after cataract extraction. The visual acuity of pseudophakic JIA eyes was significantly better up to 7 years after cataract extraction compared to aphakic JIA eyes. No cocoon formation round the intraocular lens was observed. Phthisis was found in only 1 aphakic JIA eye and hypotony only occurred in an aphakic JIA eye. The number of complications between pseudophakic JIA eyes and pseudophakic non-JIA eyes did not differ during the first 3 years after cataract extraction. One year after cataract extraction, the visual acuity was significantly better in the pseudophakic JIA group than in the pseudophakic non-JIA group.

We conclude that with maximal control of inflammation and intensive follow-up, intraocular lens implantation in children with JIA-associated uveitis is not associated with an increased risk of ocular hypertension, secondary glaucoma, cystoid macular edema or optic disc swelling and shows better visual results up to 7 years after cataract extraction than the aphakic eyes of children with JIA-associated uveitis.

In **chapter 6** we analyze, using a multiplex immunoassay, 16 immune mediators in the aqueous humor of 25 children with uveitis and 6 children without uveitis in order to identify the factors that mediate the immune response in the pediatric eye. In this clinical laboratory investigation we found significantly higher levels of interleukin-2 (IL-2), IL-6, IL-10 IL-13, IL-18, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), soluble intercellular adhesion molecule 1 (sICAM-1; CD54), RANTES (Regulated on Activation, Normal T-cell Expressed, and Secreted; CCL5), IL-8 (CXCL8) and interferon-inducible 10kDa protein (IP-10; CXCL10) in children with uveitis than in children without uveitis. The levels of IL-1β, IL-4, IL-12 p-70, soluble vascular cell adhesion molecule 1 (sVCAM-1; CD106) and Eotaxin (CCL11) did not significantly differ in the aqueous humor of uveitis patients compared with controls. Lower levels of IL-10 and IL-8 were found in quiescent stage (surgical) uveitis samples (n=16) compared with active (diagnostic) uveitis samples (n=9) and in samples from patients treated with methotrexate (MTX, n=11) compared with samples of patients not treated with MTX (n=14). Lower

levels of IL-10 were also found in samples taken during the first 3 months after the diagnosis of uveitis (n=10) than in samples taken later during the disease process (n=15). In eyes with chronic uveitis (n=21) the aqueous humor levels of IP-10 and IL-2 tended to be higher than the levels in aqueous humor of eyes with acute uveitis (n=4, not significant).

We conclude that a spectrum of cytokines, chemokines and soluble adhesion molecules in the aqueous humor of children with uveitis is involved in the pathogenesis of uveitis. These mediators are present irrespective of active or inactive uveitis and without clear predominance of a Th1- or Th2-associated cytokine profile.

In **chapter 7** we analyze the aqueous humor of children (n=12), adolescents (n=16) and adults (n=35) with uveitis for IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p-70, IL-13, IL-18, IFN-γ, TNF-α, sICAM-1, sVCAM-1, RANTES, Eotaxin and IP-10 to determine the immune mediator profile in relation to age in patients with uveitis. We found significant differences between the 3 age groups for the concentration of 13 out of all 16 mediators, but not for IL-8, RANTES and IP-10. Twelve of these 13 mediators were found in lower concentrations in adults compared with children (not significant for IL-10) and adolescents, but IL-6 concentration was higher in adults than in children and adolescents. Between children and adolescents, no differences were found for all 16 mediators.

We conclude that different levels of immune mediator responses are present in the aqueous humor of uveitis patients in different age groups. The majority of pro-inflammatory immune mediators were present in a higher concentration in the aqueous humor of children and adolescents compared with that of adults, with the exception of IL-6.

In **chapter 8** we report a case of uveitis associated with sarcoidosis which was first diagnosed as being JIA. The girl suffered from fever, arthritis and skin rash, and presented with multiple subepithelial corneal nebulae, focal active keratitis, bilateral anterior uveitis and small conjunctival granulomas at first ophthalmologic examination. Four years later she developed renal failure and the diagnosis of sarcoidosis was made. In addition we noted focal keratitis with subsequent nebulae in 2 other children with preschool sarcoidosis.

We conclude that keratitis with multiple subepithelial corneal nebulae might occur in the early stage of sarcoidosis in children. We recommend considering the diagnosis of sarcoidosis in children with arthritis and this specific corneal involvement.

In **chapter 9** we report a case of uveitis in a 13-year-old boy who was referred because of unilateral uveitis complicated by mature cataract. No indication of a systemic disease was found by the pediatrician. The aqueous humor sample for diagnostic purposes was positive for Rubella virus and a second aqueous humor sample collected during cataract surgery was also positive for Rubella virus-specific antibody production. The parents indicated that the boy had been denied vaccination for religious reasons, but they did not recall their child having had rubella.

We conclude that a Rubella virus infection may present as isolated uveitis, later in life, and this diagnosis should be considered in unvaccinated patients.

Conclusions

The conclusion to our investigation in this thesis is that of all children with uveitis, those with JIA are at greatest risk of developing secondary glaucoma. When glaucoma surgery is required, we found that the implantation of an Ahmed glaucoma valve is more successful than trabeculectomy in pseudophakic or aphakic eyes of children with JIA-associated uveitis but in phakic eyes trabeculectomy postpones the need for a glaucoma drainage implant by several years.

Our next conclusion is that the presence of posterior synechiae at the time of diagnosis of uveitis is the major cause of the development of cataract and conversely, treatment with methotrexate early in the course of uveitis postpones the need for cataract surgery in children with JIA. If cataract surgery is required, the implantation of an intraocular lens in children with JIA-associated uveitis is not associated with an increased risk of the development of long-term ocular complications such as ocular hypertension, secondary glaucoma, cystoid macular edema and optic disc swelling, but led to a good visual outcome.

Finally, we conclude that multiple intraocular cytokines, chemokines and soluble adhesion molecules in the aqueous humor are involved in the pathogenesis of pediatric uveitis. These mediators are present without clear predominance of a Th1- or Th2-associated cytokine profile. Furthermore, higher concentrations of several pro-inflammatory immune mediators are present in the aqueous humor of children and adolescents with uveitis than in adults, with the exception of IL-6.

Considerations

We found that the implantation of an Ahmed glaucoma valve implant is a better treatment option than trabeculectomy in aphakic or pseudophakic eyes of children with JIA-associated uveitis. However, the question remains of which glaucoma drainage implant is most successful in children with (JIA-associated) uveitis and what the long-term complications are of a glaucoma drainage implant: conjunctival erosion, valve migration, tube-cornea touch and corneal decompensation?

While investigating the risk factors of cataract development we found that the early treatment with methotrexate (start of treatment during the first years after the diagnosis of uveitis) postpones the need for cataract surgery by several years. Further studies might focus on whether "late treatment" with methotrexate is capable of slowing down the development or progression of cataract formation. Furthermore, it would be interesting to examine whether alternative immunosuppressive drugs or biologics also have a protective effect on the development of cataract.

In the aqueous humor of selected children with uveitis we found lower levels of interleukin-10 (IL-10) and IL-8. Furthermore, we found higher levels of several immune mediators in the aqueous humor of children and adolescent compared to adults. For further study, examination of a large collection of aqueous humor samples of patients with the same uveitis entity might refine the above-mentioned findings. This study could also clarify whether the IL-10 and IL-8 levels in aqueous humor are related to uveitis activity, the early or late phase of the course of uveitis, systemic treatment with immunosuppressive medication, the underlying cause of uveitis or the age of the uveitis patients.

The presence of ocular complications at the time of diagnosis of uveitis is associated with a worse visual outcome. Despite the ophthalmologic screening guidelines for uveitis, many patients develop ocular complications. In recent years it was proposed that the presence of HLA-DRB1*11 might be a risk factor for developing uveitis, and the presence of elevated serum levels of $\alpha 2$-globulin at time of diagnosis of arthritis might be associated with a severe uveitis course. Therefore we would like to investigate whether more intensive screening, especially in those with the above-mentioned risk factors, leads to fewer ocular complications at the time of diagnosis of uveitis, with the aim of improving the long-term visual outcome of children with JIA-associated uveitis.

Samenvatting en conclusies

Samenvatting

Het doel van dit proefschrift is tweedelig. Ten eerste willen wij meer inzicht verkrijgen in de ontwikkeling van oogheelkundige complicaties bij kinderen met uveïtis (inwendige oogontsteking) en de behandelingsopties evalueren voor de vaak visus bedreigende situaties met speciale aandacht voor kinderen met juveniele idiopathische artritis- (JIA-) geassocieerde uveïtis **(Hoofdstuk 2-5)**. Ten tweede willen we onderzoeken welke immuunmediatoren betrokken zijn in de pathogenesis van uveïtis op de kinderleeftijd (<16 jaar) door het analyseren van het voorste oogkamerwater van kinderen met uveïtis **(hoofdstuk 6-7)**.
Tijdens dit studietraject hebben we ook twee uitzonderlijke casus beschreven van uveïtis op de kinderleeftijd. De eerste beslaat sarcoïdose als de differentiële diagnose van JIA en de tweede gaat over uveïtis bij een niet-gevaccineerd kind **(hoofdstuk 8-9)**.

Hoofdstuk 1 geeft een korte introductie over uveïtis op de kinderleeftijd met de nadruk op JIA-geassocieerde uveïtis, de complicaties, de behandelingsmethoden en aanbevelingen voor screening.

In **hoofdstuk 2** onderzoeken wij welke kinderen met uveïtis het grootste risico lopen op het ontwikkelen van oculaire hypertensie (niet schadelijke hoge oogboldruk) en secundair glaucoom (schadelijke hoge oogboldruk). Deze informatie is zeer waardevol aangezien secundair glaucoom een van de meest frequente oorzaken is van blindheid bij kinderen met uveïtis. Vijf jaar na het ontstaan van de oogontsteking vonden wij een verhoogde oogboldruk bij 35% (22/62) en secundair glaucoom bij 21% (13/62) van alle kinderen met uveïtis. Bij kinderen met JIA-geassocieerde uveïtis was het percentage secundair glaucoom bijna twee keer zo hoog (38%, 9/24). De anatomische lokalisatie van de inwendige oogontsteking was van invloed op het tijdsinterval tussen het ontstaan van uveïtis en het ontwikkelen van een verhoogde oogboldruk. Kinderen met uveïtis posterior of intermediaire uveïtis hadden een korter tijdsinterval (respectievelijk 0.3 en 0.9 jaar) dan kinderen met uveïtis anterior of panuveïtis (respectievelijk 2.3 en 2.9 jaar). Geen van de patiënten met intermediaire uveïtis en een verhoogde oogboldruk ontwikkelde echter secundair glaucoom, terwijl eenderde van de patiënten met uveïtis anterior wel secundair glaucoom ontwikkelde. Tweederde van alle kinderen met oculaire hypertensie of secundair glaucoom ontwikkelde de verhoogde oogboldruk gedurende de eerste twee jaar na het ontstaan van de uveïtis.

Wij concluderen dat JIA-geassocieerde uveïtis (inclusief ANA-positieve patiënten zonder verschijnselen van artritis) de belangrijkste risicofactor is voor het ontwikkelen van secundair glaucoom bij uveïtis op de kinderleeftijd. Naar aanleiding van dit onderzoek raden wij aan de oogboldruk van kinderen met uveïtis altijd te meten tijdens frequente controles bij de oogarts.

In **hoofdstuk 3** vergelijken wij twee chirurgische technieken voor de behandeling van secundair glaucoom bij kinderen met JIA-geassocieerde uveïtis: Ahmed glaucoma valve implantatie (buisje, 13 ogen) en trabeculectomie (luikje, 27 ogen) om uit te zoeken welke van deze twee technieken het meest succesvol is. In de Ahmed glaucoma valve groep faalde geen enkele operatie. In de trabeculectomiegroep was de gemiddelde duur van succes van de operatie 4.7 jaar. Staaroperatie bleek een belangrijke risicofactor te zijn voor het falen van de trabeculectomie. We vonden een gemiddelde duur van succes in de trabeculectomiegroep van 7.51 jaar voor niet aan staar geopereerde ogen (n=9), 1.96 jaar voor ogen met staaroperatie voor trabeculectomie (n=6) en 2.81 jaar voor ogen met staaroperatie na trabeculectomie (n=12). Als we de niet aan staar geopereerde ogen van de trabeculectomiegroep vergeleken met de ogen van de Ahmed glaucoma valve groep vonden we geen verschil in de duur van succes van de operatie. Echter, wanneer we alle aan staar geopereerde ogen van de trabeculectomiegroep vergeleken met de Ahmed glaucoma valve groep vonden we wel een significant verschil in het voordeel van de Ahmed glaucoma valve groep.

Wij concluderen dat de primaire implantatie van een Ahmed glaucoma valve in aan staar geopereerde ogen van kinderen met JIA-geassocieerde uveïtis een betere behandelingsoptie is dan trabeculectomie. Echter, in niet aan staar geopereerde ogen van kinderen met JIA-geassocieerde uveïtis kan een primaire trabeculectomie de noodzaak van een glaucoom-implant met ongeveer zeveneneenhalf jaar uitstellen.

Hoofdstuk 4 is een studie naar de risicofactoren voor het ontwikkelen van staar bij 53 kinderen met JIA-geassocieerde uveïtis. In deze studie vonden wij dat kinderen met synechiae posteriores (verklevingen tussen iris en voorste lenskapsel), een significant kortere tijdsperiode hebben tussen de diagnose uveïtis en staaroperatie dan kinderen zonder synechiae posteriores (respectievelijk 3.0 jaar versus 8.5 jaar). De behandeling met methotrexaat, gestart tijdens het eerste jaar na de diagnose van uveïtis, resulteerde in een significant langere tijdsperiode tussen de diagnose uveïtis en staaroperatie dan wanneer geen behandeling met methotrexaat was gestart (respectievelijk 7.0 jaar versus 3.5 jaar). De behandeling

met corticosteroïdinjecties bij het oog tijdens het eerste jaar na de diagnose uveïtis liet een trend zien (niet significant) van een snellere staarontwikkeling. Of systemische behandeling met corticosteroïden het tijdsinterval tussen de diagnose uveïtis en staaroperatie beïnvloedt kan niet uit onze resultaten worden geconcludeerd.

Wij concluderen dat de ontwikkeling van staar bij kinderen met JIA-geassocieerde uveïtis wordt veroorzaakt door meerdere factoren. De aanwezigheid van synechiae posteriores ten tijde van de diagnose uveïtis is sterk geassocieerd met vroege staarontwikkeling. Vroege behandeling met methotrexaat bij kinderen met JIA-geassocieerde uveïtis is geassocieerd met een vertraagde staarontwikkeling.

In **hoofdstuk 5** evalueren wij of de implantatie van een intraoculaire lens tijdens staaroperatie het risico op lagetermijncomplicaties bij kinderen met JIA-geassocieerde uveïtis verhoogt. Wij vonden geen significant verschil in complicaties, te weten oculaire hypertensie, secundair glaucoom, cystoïd macula oedeem, papiloedeem en hypotonie tussen afake (geen intraoculaire lens) en pseudofake (wel een intraoculaire lens) ogen van kinderen met JIA-geassocieerde uveïtis gedurende de eerste tien jaar na staaroperatie. De gezichtsscherpte van de pseudofake ogen was significant beter dan die van de afake ogen met JIA-geassocieerde uveïtis tot zeven jaar na staaroperatie. Rond de intraoculaire lens werd geen coconvorming gezien. Ftisis bulbi (verschrompeling van de oogbol) en hypotonie werden slechts één keer waargenomen in de afake JIA-geassocieerde uveïtisgroep. Het aantal complicaties was niet verschillend tussen de pseudofake JIA-geassocieerde uveïtisgroep en de pseudofake niet-JIA-geassocieerde uveïtisgroep gedurende de eerste drie jaar na staaroperatie. Een jaar na staaroperatie was de gezichtsscherpte significant beter in de pseudofake JIA-geassocieerde uveïtisgroep dan in de pseudofake niet-JIA-geassocieerde uveïtisgroep.

Wij concluderen dat met maximale controle van de inwendige oogontsteking en intensieve follow-up, de implantatie van een intraoculaire lens bij kinderen met JIA-geassocieerde uveïtis niet is geassocieerd met een verhoogd risico op het ontwikkelen van oculaire hypertensie, secundair glaucoom, cystoïd macula oedeem en papiloedeem, maar resulteert in een betere gezichtsscherpte gedurende de eerste zeven jaar na staaroperatie.

In **hoofdstuk 6** analyseren wij 16 immuunmediatoren in het voorste oogkamerwater van 25 kinderen met uveïtis en 6 kinderen zonder uveïtis met als doel te identificeren welke factoren betrokken zijn bij de immuunreactie in het kinderoog. Wij vonden in dit klinisch laboratoriumonderzoek significant hogere waarden van

interleukine-2 (IL-2), IL-6, IL-10 IL-13, IL-18, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), soluble intercellular adhesion molecule 1 (sICAM-1; CD54), RANTES (Regulated on Activation, Normal T-cell Expressed, and Secreted; CCL5), IL-8 (CXCL8) en interferon-inducible 10kDa protein (IP-10; CXCL10) in het voorste oogkamerwater van kinderen met uveïtis dan in het voorste oogkamerwater van kinderen zonder uveïtis. De waarden van IL-1β, IL-4, IL-12 p-70, soluble vascular cell adhesion molecule 1 (sVCAM-1; CD106) en Eotaxin (CCL11) verschilden niet tussen het voorste oogkamerwater van uveïtis patiënten en de controles. Lagere waarden van IL-10 en IL-8 werden gevonden in het voorste oogkamerwater van patiënten waarbij de uveïtis rustig was dan in het voorste oogkamerwater van patiënten met actieve uveïtis, en in monsters van patiënten behandeld met methotrexate (n=11) dan in monsters van patiënten niet behandeld met methotrexate (n=14). Tevens werden lagere waarden van IL-10 gevonden in monsters afgenomen gedurende de eerste drie maanden na het ontstaan van uveïtis (n=10) dan in monsters later afgenomen (n=15).

Wij concluderen dat een spectrum van immuunmediatoren in het voorste oogkamerwater van kinderen met uveïtis betrokken is bij de pathogenesis van deze inwendige oogontsteking. Deze mediatoren zijn aanwezig ongeacht uveïtisactiviteit en zonder duidelijke dominantie van bepaalde cellen van het immuunsysteem (Th1- of Th2-geassocieerde cytokinenprofielen).

In **hoofdstuk 7** analyseren wij het voorste oogkamerwater van kinderen (n=12), adolescenten (n=16) en volwassenen (n=35) met uveïtis op de concentratie van IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p-70, IL-13, IL-18, IFN-γ, TNF-α, sICAM-1, sVCAM-1, RANTES, Eotaxin en IP-10 om het profiel van immuunmediatoren te bepalen in relatie tot de leeftijd. Wij vonden significante verschillen in concentraties voor 13 van de 16 mediatoren tussen de drie leeftijdsgroepen, maar niet voor IL-8, RANTES en IP-10. Twaalf van deze 13 mediatoren werden gevonden in een lagere concentratie in het voorste oogkamerwater van de volwassen groep dan van kinderen (niet significant voor IL-10) en adolescenten. De concentratie van IL-6 in het voorste oogkamerwater was hoger bij volwassenen dan bij kinderen en adolescenten. Tussen kinderen en adolescenten vonden wij geen verschil voor alle 16 mediatoren.

Wij concluderen dat verschillende concentraties van immuunmediatoren aanwezig zijn in het voorste oogkamerwater van patiënten met uveïtis in verschillende leeftijdsgroepen. De meerderheid van proinflammatoire immuunmediatoren zijn aanwezig in een hogere concentratie in het voorste oogkamerwater van kinderen en adolescenten dan van volwassenen, met uitzondering van IL-6.

In **hoofdstuk 8** wordt een casus beschreven van sarcoïdose-geassocieerde uveïtis welke in eerste instantie was gediagnosticeerd als zijnde JIA. Het meisje leed aan koorts, artritis en huiduitslag. Tijdens het eerste oogheelkundig onderzoek werden multipele subepitheliale corneale nebulae, focale actieve keratitis, bilaterale uveïtis anterior en kleine conjunctivale granuloompjes gezien. Vier jaar later ontwikkelde zij nierfalen waarop de diagnose sarcoïdose werd gesteld. Bij twee andere kinderen met sarcoïdose zagen wij ook focale keratitis en nebulae.

Wij concluderen dat keratitis met multipele subepitheliale corneale nebulae zich mogelijk kan presenteren in de vroege fase van sarcoïdose bij jonge kinderen. Wij raden daarom aan de diagnose sarcoïdose te overwegen bij kinderen met artritis en deze specifieke corneale kenmerken.

In **hoofdstuk 9** beschrijven wij een casus van een 13 jaar oude jongen met eenzijdige uveïtis en matuur cataract (rijpe staar). Door de kinderarts werden geen aanwijzingen voor een systeemziekte gevonden. Het diagnostische voorste oogkamerwatermonster was positief voor Rubella virus-specifiek antilichaamproductie evenals het tweede monster, afgenomen tijdens staaroperatie. De ouders gaven aan dat de jongen, wegens religieuze overwegingen, niet was gevaccineerd, maar ook dat hij geen rodehond had gehad.

Wij concluderen dat een Rubella virusinfectie zich later in het leven kan presenteren als een geïsoleerde uveïtis en dat deze diagnose overwogen dient te worden bij ongevaccineerde patiënten.

Conclusies

De eerste conclusie van ons onderzoek is dat kinderen met JIA-geassocieerde uveïtis het hoogste risico hebben op het ontwikkelen van secundair glaucoom. Indien een glaucoomoperatie noodzakelijk is, blijkt de implantatie van een Ahmed glaucoma valve meer succesvol te zijn dan trabeculectomie in aan staar geopereerde ogen van kinderen met JIA-geassocieerde uveïtis. Echter, in niet aan staar geopereerde ogen van kinderen met JIA-geassocieerde uveïtis kan trabeculectomie de implantatie van een glaucoom-implant met meerdere jaren uitstellen.

Onze volgende conclusie is dat de aanwezigheid van synechiae posteriores ten tijde van de diagnose uveïtis de grootste risicofactor is op het ontwikkelen van staar. Vroege behandeling met methotrexaat is echter geassocieerd met een vertraagde staarontwikkeling bij kinderen met JIA-geassocieerde uveïtis. De implantatie van een intraoculaire lens bij kinderen met JIA-geassocieerde uveïtis is op de lange termijn niet geassocieerd met een verhoogd risico op het ontwikkelen van complicaties zoals oculaire hypertensie, secundair glaucoom, cystoïd macula oedeem en papiloedeem, en resulteert in een betere gezichtsscherpte.

Tot slot concluderen wij dat meerdere immuunmediatoren betrokken zijn bij de pathogenesis van uveïtis op de kinderleeftijd zonder duidelijke dominantie van bepaalde cellen van het immuunsysteem (Th1- of Th2-geassocieerde cytokinenprofielen). Bovendien zijn hogere concentraties van verschillende immuunmediatoren aanwezig in het voorste oogkamerwater van kinderen en adolescenten met uveïtis dan bij volwassenen, met uitzondering van IL-6.

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Dankwoord

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Curriculum Vitae

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De auteur van dit proefschrift werd geboren op 27 december 1975 te Drunen en groeide op in Breda, Noord-Brabant. In 1995 behaalde zij het VWO-diploma aan de Nassau Scholengemeenschap te Breda. Haar studie Geneeskunde startte zij in Antwerpen aan het Rijksuniversitair Centrum Antwerpen (huidige Universiteit Antwerpen) om vervolgens een jaar later de studie voort te zetten aan de Universiteit Utrecht. Het doctoraal en het artsexamen werden in respectievelijk 2002 en 2004 behaald. Vanaf september 2004 werkte zij als arts-onderzoeker aan haar proefschrift op de afdeling Oogheelkunde van het UMC Utrecht onder begeleiding van Prof.dr. A. Rothova, Prof.dr. J.S. Stilma en dr. J.H. de Boer. Vanaf december 2008 zal zij als arts in opleiding tot specialist werkzaam zijn op de afdeling Oogheelkunde van het UMC Utrecht.